How Can We Modulate Cytokine Production and Action?

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Introduction: Role of Cytokines in Wasting Diseases

The loss of body weight and development of cachexia are common signs associated with several diseases.

Net muscle protein catabolism is the result of a neuronal and endocrinological response, the main hormone involved in this process being cortisol [1]. Besides this, a number of pathological situations (e.g. cancer, infection, trauma, surgery) lead to activation of the immunological system which, in particular, involves the release of mediators. Among these, cytokines play a preeminent role. Cytokines are now classified according to the cell subset synthesizing them (i.e. Th1 and Th2) and their main action (i.e. pro- versus anti-inflammatory). The main Th1 cytokines are tumor necrosis factor-α (TNF-α), interleukin (IL)-1α and β and interferon-γ (IFN-γ). The main Th2 cytokines are IL-4 and IL-10. A notable exception to this classification is IL-6, which is synthesized by Th2 cells but is more a proinflammatory cytokine (PIC) [2]. Th1 cytokines inhibit Th2 cytokine production and vice versa.

PICs contribute to protein wasting via several mechanisms, including a direct effect on: (i) protein turnover (i.e. net protein catabolism) increasing protein catabolism through NF-κB activation [3] and activation of the ubiquitin-proteasome system [4, 5], especially activation of E3 ligases atrogin-1 and MURF-1 [6–8], decreasing protein synthesis through inhibition of eIF2Be [9] or other factors involved in the translation process such as 4E-BP1 [10], and (ii) amino acid metabolism and oxidation through gluconeogenesis [11]. Also, cytokines potentiate cortisol and glucagon action at the target tissue level (i.e. muscle and liver, respectively) and blunt IGF-1 production and action in muscle [6]. However, the problem is complicated by the fact that each individual PIC has a more or less significant effect on specific aspects of protein
metabolism (e.g. protein catabolism, protein synthesis, amino acid oxidation or tissue efflux) [12].

There are very few studies concerning the production of cytokines and its consequences in patients under long-term artificial nutrition at home, but there is no reason to think that this may be different from what happens at the hospital once the disease evolves. In a recent study, Hise et al. [13] studied well-nourished stable patients on home parenteral nutrition (10 short bowel syndrome, 2 dysmotility syndromes). TNF-α, IL-6 and C-reactive protein plasma levels were not different from controls. However, soluble TNF-α receptors p55 and p75 and sICAM-1 were significantly higher. This suggests that even in stable well-nourished patients the method of feeding may alter the immunological status and thus nutritional status.

In this short review, various means for modulating PIC are discussed, focusing specifically on the regulation of protein metabolism. Occasionally, the effects of manipulations on survival are described. In order to remain as clear as possible, manipulations are described according to the target (i.e. cytokine production, cytokine action). Figures 1 and 2 summarize the regulation of cytokine synthesis and actions.

**Limiting PIC Production**

It is possible to counteract PIC production using physiopathological approaches. Cortisol exerts a retro-inhibitory effect on PIC synthesis [14]. However, the use of glucocorticoids to inhibit PIC synthesis is unsuitable as an anti-cachexia therapy since glucocorticoids themselves are potent inducers of protein catabolism [14].

Several drugs are able to decrease PIC production. Among them, pentoxifylline (PTX), a phosphodiesterase inhibitor, has been the most extensively studied. PTX inhibited TNF-α production, restored IL-2 synthesis and improved survival in a burn-injury mouse model [15]. In a model of rats infected by living *Escherichia coli*, PTX suppressed the increase in plasma concentrations of TNF-α, and partially prevented the inhibition of protein synthesis [16, 17] and stimulation of protein degradation [16]. Finally, PTX decreased anorexia, but the effects on protein turnover described above were not dependent on food intake [17].

The action of PTX does not seem to be related to antioxidant properties since this drug failed to modify the glutathione decrease and malonyldialdehyde increase in a model of liver ischemia/reperfusion injury [18].

Curcumin (diferuloylmethane) is a dietary pigment that gives curry its yellow color. Its action relies on its ability to block the activity of the NF-κB inhibitor, IκB [19] or upstream at MEKK-1 level [20] (see fig. 2 for details about NF-κB processing and action). Curcumin administration stimulates
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Fig. 1. A simplified presentation of cytokine processing and action, and how drugs or nutrients can interfere with cytokine production or action. Stimuli such as LPS lead to reactive oxygen species (ROS) and NF-κB activation (see figure 2 for details), leading to gene transcription and cytokine synthesis. Cytokines bind to ubiquitous receptors eliciting signals responsible for alterations in protein metabolism. Cortisol may potentiate certain actions of cytokines. Drugs and nutrients can interfere at every step of the process. GLN = Glutamine; CYS = cysteine; GLY = glycine; ALLN = N-acetyl-leucinyl-leucinyl-norleucinal; ab = antibody; ra = receptor agonist; rab = receptor antibody; Cox = cyclooxygenase; ARA = arachidonic acid.

muscle regeneration after injury [19]. Curcumin inhibits IL-1β-mediated ICAM-1 and IL-8 gene expression in intestinal cells [20].

N-Acetyl-leucinyl-leucinyl-norleucinal (ALLN) is a potent inhibitor of proteolysis catalyzed by proteasomes. By this mechanism, ALLN inhibits the degradation of IκB and the proteolytic cleavage of p105 to p50 and therefore the formation of the active p50/p65 NF-κB heterodimer [21]. Hence, ALLN counteracts IL-6 and TNF-α production by macrophages in vitro or in vivo in response of mice to LPS [21].

Cloricromene is a semi-synthetic non-anticoagulant coumarine derivative with anti-platelet and anti-leukocyte properties. Cloricromene inhibits LPS-induced TNF-α release by rat macrophages in a dose-dependent manner and inhibits LPS-induced expression of TNF-α mRNA [22]. In addition, in this situation cloricromene inhibits NF-κB activation as a result of an inhibition of LPS-induced cellular oxidative activity [22].
Various inflammatory mediators, including IL-6 and TNF-α, cause a cascade of events which lead to phosphorylation of IκB and its degradation. NF-κB is then free to translocate to the nucleus, thereby initiating transcription for various PICs, iNOS and adhesion molecules [23]. In a model of endotoxemic shock, isoheleenin, a sesquiterpene lactone, inhibited nucleus translocation of NF-κB without modification of IκB degradation. Interestingly, plasma NO′ was lower and survival was higher in isoheleenin-treated animals [23].

**Limiting PIC Interaction with Target Cells**

The administration of antibodies against PIC will neutralize them. Hence, the administration of an anti-TNF-α IgG to tumor-bearing rats decreased protein degradation rates in skeletal muscle, heart and liver compared with controls [24], and this action may be related to the fact that TNF-α antibody abolishes the increase in muscle ubiquitin gene expression observed in cancer-bearing animals [5]. However, blocking TNF-α with antibodies may prove detrimental: for example, in rats with caerulein-induced pancreatitis, blockade of TNF-α activity was found to increase edema formation in both the pulmonary and pancreatic microvascular beds [25].
Antibodies directed towards PIC receptors can also be used. Hence, in a model of lethal endotoxemia in mice, murine monoclonal IL-1 receptor antibody (IL-1rab) dramatically improved survival [26]; of note, both plasma IL-6 and IL-6 gene expression in the liver were decreased in IL-1rab-treated animals [26]. In a very elegant and interesting study, Tsujnaka et al. [27] showed that mice overexpressing IL-6 exhibit muscle atrophy and that treatment with IL-6 receptor antibody totally counteracted the effects of IL-6 on muscle weight and cathepsin activity.

IL-1 receptor antagonist (IL-1ra) is produced by lymphocytes and phagocytes; its amino acid sequence is very similar to that of IL-1 and it blocks both type-I and type-II IL-1 receptors without exhibiting any agonist activity [28]. In an experimental model of endotoxemia in rats, it was shown that recombinant IL-1ra administration blunts the increase in LPS-mediated protein breakdown [29]. In a model of chronic abdominal sepsis, IL-1ra administration counteracted the sepsis-induced decrease in the rate of protein synthesis in muscle [30].

Another way to block PIC action is to block the cortisol receptor, since the interaction between PIC and cortisol at the target cell receptor level could potentiate the effects of both molecule types. However, RU 38486 failed to block IL-1-induced muscle proteolysis [31]. That said, the effect may be different from one PIC to another. For example, whereas both TNF-α and IL-1 administration inhibit amino acid uptake by rat muscle, only TNF-α action was counteracted by RU 38486 [32].

**Blockage of PIC Message within Target Cells**

PICs activate PGE2 synthesis in skeletal muscle, which in turn may activate lysosome-mediated proteolysis. However, indomethacin, an inhibitor of cyclooxygenase, failed to counteract the augmentation of amino acid leg efflux in septic patients [33]. In contrast, perioperative ibuprofen administration in patients undergoing cholecystectomy blunted hyperglycemia and led to smaller changes in IL-6, ACTH and cortisol than in controls, whereas C-reactive protein was similar in the 2 groups [34].

**Limiting PIC Production and Action with Anti-Inflammatory Cytokines**

The main anti-inflammatory cytokines are IL-4 and IL-10. As mentioned above, these cytokines are produced as a result of immune activation by a subpopulation of helper T cells (Th2) and inhibit the production of PICs by Th1 cells. Hence, IL-10 administration reduced lung dysfunction and mortality in a murine model of multiple organ dysfunction induced by zymosan.
treatment [35]. More specifically, LPS (from *E. coli*, 10 mg/kg) administration to rats decreased the force-frequency curves and half-relaxation time of the diaphragm muscle. When IL-10 was injected intraperitoneally 5 min after LPS, LPS-mediated effects were counteracted, and this was associated with a significant decrease in NO production [36].

However, because of the broad immunosuppressive and anti-inflammatory properties of IL-10, its potential for resulting in secondary infections is a matter of concern: administration of IL-10 may suppress T-cell function and further increase the risk of opportunistic infections in patients with preexisting immune suppression [37]. Moreover, blocking IL-10 production by using a chemical agent (e.g. AS101) can either improve or worsen survival of mice in a model of cecal ligation and puncture, depending on the time of administration [38].

**Effects of Specific Nutrients**

*Glutamine (GLN)*

There are several studies supporting evidence that GLN (in GLN-enriched parenteral nutrition) acts as an anti-inflammatory agent. For example, De Beaux et al. [39] showed that total parenteral nutrition enriched with GLN blunts the IL-8 response to stress in patients with pancreatitis.

Given that GLN is a key substrate for activated immune cells, it is not surprising that in vitro GLN availability modulates cytokine production. However, diverse results have been obtained: e.g. an increase in IL-1 production [40] or a decrease in TNF-α production [41] by macrophages in response to increasing GLN levels in the medium. This variability is dependent on several factors.

1. The agent (e.g. concanavalin A, LPS) used to stimulate cells [42].
2. The amount of arginine in the culture medium [41]. In fact, arginine-derived nitric oxide production can interfere with GLN action, since nitric oxide is also a potent modulator of NF-κB.
3. The cell type: the production of anti-inflammatory cytokines by T-lymphocytes is highly stimulated by GLN, and in parallel the production of PICs by monocytes is significantly less stimulated [42]. Hence, GLN action is the result of modulation of anti-inflammatory/inflammatory balance.

Interestingly, the GLN effect is not limited to immune cells: biopsies of human duodenum in culture release less IL-6 and IL-8 when incubated with GLN compared to GLN-free conditions [43]. In addition, when biopsies are incubated in the presence of IL-1, GLN dose-dependently decreased the IL-1β-mediated increase in IL-6 and IL-8 production [44]. In Caco-2 cells, GLN blunted LPS-mediated IL-8 production and this effect was not related to NF-κB [45].

These effects of GLN could be direct, depending on the regulation of cell volume for example, or indirect, related to the production of key molecules,
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e.g. inhibiting nitric oxide production [46] or activating glutathione synthesis. As a matter of fact, GLN forms the precursor pool of glutamate, which is involved in glutathione synthesis, the major antioxidant system. In postoperative patients, GLN supplementation of total parenteral nutrition counteracts the injury-related decrease in total and reduced glutathione [47]. Glutathione is actually a repressor of NF-κB activation [28], the main transduction factor mediating PIC action.

**n-3 Fatty Acids**

Production of cytokines and their cellular effects is mediated and modulated by a number of compounds formed from the hydrolysis of membrane phospholipids by phospholipases A2 and C, and by activation of protein kinase C. Hence, alterations in phospholipid fatty acid composition will change the nature of substrates for the action of phospholipases [28], leading to the production of different eicosanoids with variable pro- or anti-inflammatory properties. n-3 polyunsaturated fatty acids (PUFAs), derived from linolenic acid, inhibit PIC production whereas n-6 PUFAs increase it [6].

This could explain why fish oil supplementation of the diet of patients with pancreatic cancer cachexia has been reported to stop weight loss [28].

In patients with sepsis, parenteral nutrition with fish oil resulted in lower PIC production by activated mononuclear leukocytes compared to cells from patients perfused with a conventional (n-6) lipid emulsion [48].

**Others**

In vitro, but at dosages compatible with physiology, vitamin C inhibits the activation of NF-κB by IL-1 and TNF-α in endothelial cells. This action is related to an inhibition of phosphorylation and degradation of IκBα [49].

Other antioxidants such as vitamin E, zinc and selenium are able to decrease PIC production by quenching reactive oxygen species production, and thus limiting the activation of transcription factors (e.g. NF-κB, NF-IL-6) [28].

Conversely, the production of TNF-α by mice and IL-1 by rats in response to endotoxin is suppressed by desferrioxamine, an iron chelator [28].

**Conclusion**

There are a number of experimental studies but none of the agents potentially able to modulate PIC production and/or action has proven its efficacy in regulating muscle hypercatabolism in stressed patients. In some cases, we are even faced with a yin-yang situation: whereas anti-glucocorticoid receptors blunt protein catabolism, glucocorticoids themselves repress PIC production. The association of cytokines, different dosages and timely administration may also influence the final result of the manipulation [50]. The fact that there are a number of players in the game acting as a network with
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numerous positive or negative regulatory loops further complicates the clarification of the usefulness of manipulations. Therefore, manipulating the inflammatory/immune response to stress presents a risk of serious unexpected and uncontrolled side effects, especially in the long-term. Therefore, further mechanistic studies are warranted before we can expect safe and efficient clinical application of the modulation of PIC production and action using drugs or antibodies. In contrast, the use of modulating nutrients (e.g. GLN and n-3 PUFAs) appears to be safe and efficient.

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References

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Discussion

**Dr. Bowling:** You mentioned at the beginning that your talk was about modulating cytokines and then you said why should we do it. These are clearly mechanisms essential for homeostasis. Is it therefore going to be that by looking at all the various pathways and the various kind of stages that you can intervene, that if you block one pathway or another you are simply going to upregulate or downregulate the system elsewhere, and in terms of therapeutic potential, do you actually think there is going to be an awful lot to be achieved?

**Dr. Cynober:** That is the point. If, for example, you are blocking tumor necrosis factor (TNF), you can expect to decrease some specific pathways in certain conditions, but then you must be aware than TNF in the short-term has the possibility of stimulating the production of other cytokines, for example IL-8. Up to now it is alright, it is good to limit or to block TNF production, but in the middle term there are some regulatory effects which in the end make TNF block the proinflammatory response and block the response of some other cytokines by some other cells. Therefore by doing that some other pathways are de-repressed and the reverse effect to that expected occurs. I am not really confident that in the near future, even using modern tools such as transgenic mice, we will have a definite answer about what is the target because, as I mentioned, it is a total network and when you are making something somewhere you have unexpected effects in another tissue or another organ.

**Dr. Elia:** The situation may even be more complex than you have indicated for a variety of reasons, one of which is the genetic cytokine polymorphism. There is a growing list of associations between high producers and low producers or both pro- and anti-inflammatory cytokines, which means that there is a differential response to injury according to the individual’s genotype. Do you think there is information to show that there is a differential response to treatment according to the genotype of individuals?

**Dr. Cynober:** Of course it has been demonstrated as you mentioned for example for TNF that perhaps 10–20% of the Caucasian population overexpress TNF production
and this overexpression of TNF is clearly associated with poor prognosis in intensive care units. More recently this consideration has been extended to cardiovascular disease that in the end is an inflammatory chronic disease. As I mentioned before, I think that this is a possibility of the near future to screen the patients upon entrance to the intensive care unit to determine whether or not they are suitable for specific immunomodulatory treatment. This is the first point, but note that in some cases the polymorphism is protective. This has been demonstrated for IL-6 which protects the patients against malaria complications. Now the second part of the question: Grimble [1] in Southampton made some studies showing that the ability of n-3 fatty acids to avoid inflammatory properties may be dependent upon the gene polymorphism. Perhaps you know better than I do.

Dr. Elia: I know that work very well. But of course if one is going to extend this, for example, to the intensive care unit or specific conditions, such as malaria, it is necessary to demonstrate that the results of the interventions differ either in a clinically beneficial or a negative way, according to the genetic polymorphism. I think that perhaps more work still needs to be done.

Dr. Cynober: But if it was the sense of your question, I am not aware of similar results in the field of amino acid therapy, for example arginine or others.

Dr. Lochs: Isn’t it the case that whatever we eat or feed a patient, we are interfering with cytokine production? We have a lot of information about specific substrates, if you eat long-chain triglycerides or unsaturated medium chain or if you feed more glycine or more glutamine. Are we still in the position that we can close our eyes to this information and feed a patient a so-called standard food or do we have to decide and say well, in this situation, let’s say sepsis, we do not give this and this because we know this has this and this consequence? In another situation, let’s say inflammatory bowel disease, we have good information that this and this composition is improving, and in alcoholic liver disease we have good information that this and this composition is improving. So is it still possible that in a hospital we just say well, there is some standard enteral food and let’s give it to everybody, and there is some standard composition of parenteral food, or do we have to make a more detailed recommendation based on these data you presented?

Dr. Cynober: It is a problem of a disease-specific regimen. It was not my purpose to say that. If I take the best example which is glutamine, because it is safe and was demonstrated to be efficient in a number of situations, we can now say alright, glutamine must be added as a pharmacological drug, not only as a nutrient, to patients in intensive care units in certain postoperative situations, and why not in patients with sepsis. On the contrary we can say that to date nobody has shown interest in providing glutamine in Crohn’s disease, which is another form of inflammation. I think that we can start to make a number of statements and make recommendations for the use of such drugs or pharmaconutrients or specific nutrients. But we need evidence, we need data, not speculations. Just an example, and I will be very provocative, can you explain why in the same diet huge amounts of n-3 fatty acids, which may be immuno-suppressive, and arginine, which is immunostimulative, are provided? It is provocative but we can argue like that, it is simply the period in the evolution of the patient that will indicate that such products may be useful or harmful, but we need data.

Dr. Biesalski: I think we have to keep in mind what we are dealing with: nutritional pharmacology. Let me give you an example which fits cytokine production relatively well. Retinoic acid critically regulates the expression of the redox-sensitive transcription factors like AP1 and NF-κB, but it would not make any sense to give vitamin A as a precursor because it is absolutely metabolically regulated. I think we have to keep in mind what we are doing, whether we give the active metabolite, for example with respect to vitamin D you have the same, they interact with the cytokine
production, or we give a nutrition where we have the pre-drug or whatever. Another example is the interaction that Grimble [1] showed, this nice balance of antioxidants and NF-κB activation. If you give β-carotene as provitamin A it fulfills two roles as an antioxidant and probably as vitamin A precursor in another way because it circumvents the metabolic control of vitamin A via the liver. So I think we should also address the question what is nutrition on the one hand and what is probably circumventing metabolic pathways and can be useful to interact with processes like this. I have one question: do you have any evidence or know of a clinical study with cytokine production and retinoic acid? It would make sense from basic knowledge and from in vitro animal experience.

_Dr. Cynober:_ I confess my ignorance. It is out of my major field of interest. I don’t know.

_Dr. Thomas:_ There are a number of drugs that are becoming available that are sort of anti-cytokine in a general sense, for example in inflammatory rheumatologic diseases such as cardiac cachexia.

_Dr. Cynober:_ Which drug?

_Dr. Thomas:_ The one that is available for cardiac cachexia, I think it is Inalopret, it is only available in Europe, not in the USA. Can you comment on the empirical data showing that the use of some of these anti-cytokine drugs have an effect to produce weight gain and improve nutritional parameters in these patients when they use them?

_Dr. Cynober:_ It depends on the type of drug. For example you mentioned on the first day of the meeting the possible use of statin to modulate cytokine production, and this has nothing to do directly with cholesterol. In fact, just as an example, it has an indirect effect because statin increases the activity of nitric oxide synthesis in the endothelium, which in turn allows generation of a higher quantity of nitric oxide and in this given condition it is very helpful because it will decrease the amount of oxidized low-density lipoprotein. Therefore that is a clear example of pharmacological nutrition, and you can provide both arginine and statin. We made the experiment in hypercholesterolemic rabbits, and by associating the statin and the arginine there is a dramatic effect. I am absolutely not certain that the therapy will be useful to modulate muscle protein metabolism and so on. In my opinion the larger the target, the more you will be efficient and the more side effects you will have; the more the target is limited, the more you will have specific effects and few side effects.

_Dr. Ockenga:_ Ten years ago we did a study in HIV patients with wasting and tried to use ketotifen as anti-TNF treatment [2], and indeed in the pilot study we showed a decrease in TNF released and stimulated with lipopolysaccharide, and we saw an effect on weight gain in this small clinical study. There are some other studies with thalidomide as well as pentoxifylline in AIDS patients [2] and a small clinical effect was seen. But I see some danger in using anti-TNF. Probably most of us know the study on septic patients in the intensive care unit using a TNF antibody [3]. There are 2 large acute studies showing an increased mortality using TNF antibody in this specific clinical situation [3]. So probably we have only a very limited therapeutic window we can use and we have to choose between the side effects and the effects we have on the nutrition side.

_Dr. Cynober:_ This reminds me of another study by Takala et al. [4] about the administration of human growth hormone to patients in the intensive care unit. This large multicenter trial had to be stopped because the mortality was higher in the human growth hormone-treated group. Now nutrition was rather hypocaloric and hypoproteic, and a possible explanation is that blocking protein catabolism and efflux of amino acids from the muscle completely starves the splanchnic tissues, i.e. the liver and intestine. This is another aspect. Again should we block cytokine production?
Dr. Labadarios: Thank you for your welcome comments, cautions and the philosophy of what we should or should not do. Of particular interest to me are all these new compounds that you mentioned because there is this a shift from the orthodox to a complimentary type of medicine containing plant extracts and similar compounds. In the experiments that you conducted and apart from the measurements that you showed, did you actually include, anything in terms of clinical outcomes? Let me tell you why I am asking this question. Some 10 years ago there was an article from Japan [5] that made an impression on me in the sense that they did something very simple. They made a surgical incision in rats and then fed them with an n-3-rich diet. There was no difference in the healing time as best as I can remember, but when they actually measured the strength of the wound it was significantly diminished both in terms of elasticity and strength. So apart from the things that you mentioned, are there any other such data in relation to what you presented?

Dr. Cynober: Do you mean about exotic medical products or in general? There are a lot of data in the literature and most of them are of course experimental studies for various reasons. Specifically to comment on the study on the n-3 fatty acids in wound healing in rats. I am not surprised at all because these lipids may be immunosuppressive. Now to have wound healing you need the migration of immune cells into the wound and also the release of proinflammatory cytokines, but not only, in order to synthesize new collagen and so on. I am not saying we must not use n-3 fatty acids, I am saying that probably the use of these various therapeutic agents is time related, and if you make some manipulations at not the most adequate time you can achieve a true disaster. Now there are plenty of studies with burn rats, with lipopolysaccharide-treated rats, looking at different pharmacological effects, I just made a selection.

Dr. Roessle: I wonder whether you would agree to adding the amino acid cysteine to the list of logical ingredients? As glutamine, it is a precursor of glutathione and, in the same animal model as you have shown for the data on pentoxifylline, it has been shown to downregulate TNF-α and IL-6 production without shutting them off. It also shows improved long-term outcome on sepsis, and it would be a more logical nutritional ingredient which we might consider to use in the future.

Dr. Cynober: I totally agree, and if you look at the abstract book, cysteine is mentioned together with glycine. Of course there are a lot of studies [6], especially using the stable precursor form acetylcysteine, which demonstrate that you can decrease the activation of NF-kB by mainly stimulating glutathione synthesis, but perhaps not only.

Dr. Lesourd: Don’t you think that the side effects you observed in the assays are probably related to some concept that was really wrong? We tried to block some reactions and the problem is probably not to block it but to decrease it in order for the body to go back to its own equilibrium. Probably we have been going too far in the treatment we have given in the different assays. What do you think?

Dr. Cynober: Yes, it makes sense. I will give another example of how with nutritional manipulation you can achieve something or exactly the reverse. If, for example, you use rats and take the liver and store it at 4°C and then reperfuse the stored liver, you have a certain degree of ischemia reperfusion injury. Now if you starve the rats for 2 days before taking the liver you have a huge ischemia reperfusion injury simply because you have decreased the antioxidant defenses. Now, if you starve the rats for 8 days you have no reperfusion injury simply because you have depleted the Kupfer cells and there is no longer a reaction (Charrueau, personal commun.).

Dr. Lesourd: So we are probably doing the same when we are refeeding the patients. We would like to continue the same regimen any time and that is probably not the right way to do it.

Dr. Cynober: I agree.
Dr. Elia: A growing number of amino acids have been proposed for immunonutrition and you mentioned some of them. My question is rather the opposite: are there any amino acids that you would avoid or reduce for a treatment?

Dr. Cynober: For cytokine activation and things like that?

Dr. Elia: Yes, or in terms of either laboratory or clinical studies.

Dr. Cynober: We can talk all night about protein requirement in the trauma situation and competition between amino acids. To answer your question, there is an amino acid I have almost not discussed during this presentation and that is arginine because there is a close relationship between arginine provided by food intake and the capacity to synthesize nitric oxide. This has been well demonstrated by several investigators [7]: the low part of de novo synthesis in the ability to generate nitric oxide. Of course in certain situations of overexpression of proinflammatory cytokines, overexpression of inducible nitric oxide synthesis, in patients with multiple organ failure, unstable hemodynamics, I think that large amounts of arginine may be detrimental. But in my opinion these are extreme situations, but it does not mean that I agree with Heyland et al. [8] who probably extrapolate too much data from the literature. But in certain situations, to answer to your question, yes, I think that extra arginine may be detrimental, overstimulating the immune system.

Dr. Biesalski: Can I make a short comment on that because you mentioned vitamin C and the Takala et al. [4] study. I think burn injury is an absolute contraindication for arginine because there is a massive formation of superoxide anions and if nitric oxide production is increased you get peroxynitrite and neutralization of proteins. The action of vitamin C lowers nitric oxide production and is effective in preventing edema formation. So additional arginine might be not beneficial.

Dr. Cynober: The comment on vitamin C is well taken. With regard to arginine I don’t know because specifically in burned rats there is no morbidity or mortality related to extra arginine provision, which is contrary to data obtained in peritonitis.

References