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## Arginine/Nitric Oxide Metabolism in Surgical Oncology

Buijs, N.

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## Summary

The objective of this thesis was to gain insight in the role of the arginine/NO metabolism in surgical oncology, from molecular level to whole-body level. In PART I background information on the arginine and its derivatives is provided and the physiological arginine/NO pathway is further elucidated. Arginine and its precursors have been shown to be essential pharmaco-nutrients due to their immune enhancing capacities (CHAPTER TWO). An adequate immune response is particularly important in patients undergoing surgery for recovery from injury and combating various diseases. A surgical intervention causes stress with subsequent catabolic effects on the body's substrate stores. Glutamine, the precursor of arginine, functions as fuel for rapidly dividing cells, especially cells of the immune system. Also, it activates protective mechanisms of the host because it is an important precursor for antioxidants and it improves intestinal function. Moreover, arginine is the substrate for T-lymphocytes and the sole precursor for NO production, both essential for the immune system. Supplementation of these pharmaco-nutrients in surgical patients may improve clinical outcome, since these nutrients become deficient fast under the influence of surgical stress and in disease states.

Glutamine is the precursor for arginine and glutamine supplementation augments an increase in arginine levels in healthy subjects. We designed a stable isotope study to determine the effect of intravenous glutamine supplementation on arginine production from glutamine and citrulline (CHAPTER THREE AND FOUR). It was found that an intravenous glutamine supplement in patients undergoing abdominal surgery doubles renal arginine production.

PART II of this thesis focuses on arginine/NO metabolism in surgical oncology. The nutritional status of patients is a major prognostic factor. Especially cancer patients may develop a severe catabolic state, also called cancer cachexia (CHAPTER SIX). The presence of cachectic and sarcopenic symptoms is significantly related to survival in oncologic patients. It was hypothesized that part of the pathological changes in cancer cachexia can be ascribed to an arginine deficiency state, leading to excessive changes in amino acid metabolism. It is shown in previous studies that the tumor-bearing host accelerates arginine's intestinal-renal axis by glutamine mobilization from skeletal muscle and this may promote cachexia. In CHAPTER SEVEN we describe a metabolic flux study in rats with advanced cancer cachexia. Amino acid fluxes and net fractional extractions across intestine,

kidneys, and liver were studied. In the advanced cachectic tumor-bearing state, an increase in intestinal glutamine uptake is not accompanied by an increase in renal arginine production. The adaptations found in the cachectic, tumor-bearing rat did not depend on glutamine availability.

An arginine deficiency state is typically found in tumor-bearing patients, and this diminishes immune responses against malignant degeneration. In CHAPTER EIGHT a randomized trial on the clinical effect of arginine supplementation in surgical oncology is outlined. In this double-blind trial, we randomly assigned severely malnourished patients with head and neck cancer to receive a standard perioperative enteral nutrition or an arginine-supplemented perioperative enteral nutrition. We did not observe significant differences in baseline characteristics. The group receiving an arginine-enriched diet had a significantly better overall survival and a significantly better locoregional recurrence-free survival. This supports the thought that arginine availability is particularly important at the moment one requires the most of the immune system for recovery from surgical injury and to encounter remnant malignant cells in the perioperative period.

The function of both arginine and NO are elaborately studied in the tumor environment. However, the role of other mediators in the arginine/NO pathway in surgical oncology is poorly represented in literature. NO production depends on arginine as substrate and asymmetric dimethylarginine (ADMA) as inhibitor. Dimethylarginine dimethylaminohydrolase (DDAH) catabolizes ADMA, and hereby regulates NO production. Solid tumors need vasculature to evolve and therefore angiogenesis is an essential part of cancer development. Vascular endothelial growth factor (VEGF) is a crucial component in cancer angiogenesis and uses NO as a mediator. To study the role of ADMA and DDAH in the angiogenetic pathway of primary liver cancer, we analyzed the resection specimens of twenty patients (CHAPTER NINE). Our results indicate that DDAH expression is increased in human hepatocellular carcinoma, which is associated with an increase of the arginine/ADMA ratio and enhanced NO formation. The increased DDAH expression is initiated by hypoxia and is associated with promotion of the expression of the angiogenesis stimulating factor VEGF. This suggests that DDAH might be a potential target in novel therapeutic agents and future studies are warranted to investigate the role of the arginine/NO pathway with all its mediators in cancer development and anti-cancer strategies.