Summary

The first part of the theses describes the changes in the metabolic pathway of arginine- nitric oxide using a model of acute lung injury (ALI) induced by bacterial lipopolysaccharide (LPS) in Wistar rats. ALI was induced by *i.p.* or *i.t.* administration of 5 mg/kg LPS (*Escherichia coli*, serotype O55:B5). The observational period was terminated at 3, 6 and 24 hrs following the administration. After that, the expression was studied at mRNA and protein levels of inducible and endothelial NO synthases (eNOS, iNOS), arginase 1 and 2 (ArgI, ArgI), and of cationic amino acid transporters (CAT) in lung and liver tissue, Experimental work also included the monitoring of exhaled nitric oxide (eNO) and arginine concentrations in plasma and bronchoalveolar lavage fluid (BAL). The model was further characterized by biochemical markers, the indices of alveolo-capillary membrane permeability, the presence of inflammatory cells and the concentrations of oxidative and nitrossative stress markers in the airways.

After *i.p.* injection of LPS, a profound increase occurred in exhaled eNO and NOx concentrations in BAL and plasma. The increase in eNO was observed already in 2 hr following LPS application and its maximum was >30fold above the controls. After *i.t.* application, there were signs of increased oxidative stress in the airways (MDA in BAL). Compared with *i.p.* application, greater infiltration of leukocytes and neutrophils in the airways and a higher concentration of total protein in the BAL were detected. Regardless of the route of administration, LPS induced iNOS mRNA and protein expression in lung tissue.The eNOS mRNA in the lung was significantly lower than in controls. As early as at 3 hrs following LPS administration, the expression of ArgI, ArgII and CAT1, -2 and -3 was augmented in the lungs at the mRNA level. The magnitude of ArgII induction was significantly higher than that of ArgI. After *i.t.* administration of pentoxiphylline (PX) combined with *i.t.* LPS, the increase was abolished of the eNO and NO_x concentrations in the plasma and BAL. Furthermore, the protein expression of iNOS in the lung and liver was attenuated.

Another part of the theses was devoted to a model of ovalbumin (OVA)-induced allergic airway inflammation in Brown-Norway rats. Sensitization of rats was carried outusing OVA in combination with the adjuvant Al $(OH)_3$. The development of allergic inflammation was confirmed by the increased number of white blood cells and, in particular, of the percentage of eosinophils in BAL. Moreover, the permeability of the alveolo-capillary membrane increased and the concentration of MDA and NO_x in BAL were elevated. Monitoring of mRNA and protein expression in the lung tissue showed an induction of iNOS and eNOS. Both the ArgI and ArgII enzymes were induced in the lungs at the mRNA level. However, only the ArgII protein was markedly increased and the elevation of ArgI in the lungs was marginal. An increased expression at the mRNA level was found of the transporters CAT1 and -2 in the lung and liver tissues.

The third part of the theses presents, for the first time, the data on the pharmacokinetics of the arginase inhibitor N^{ω}-hydroxy-nor-arginine (norNOHA). The bioavailability was studied in the Wistar rats after single intravenous and intraperitoneal injections and, after intratracheal application of the aerosol. The pharmacokinetics were linear after *i.p.* and *i.v.* doses from 10 to 90 mg/kg. The parameters AUC and C_{max} increased almost in proportion to the dose. The decrease in norNOHA plasma concentration was biphasic and rapid: the concentration at 20 min was less than 10 % of the initial one. The unknown metabolite of norNOHA which eluted during HPLC of plasma extracts was identified as nor-arginine with the help of mass spectrometry. Formation of this metabolite was not observed when norNOHA was incubated with whole blood or plasma *in vitro*. The second pharmacokinetic study was focused on the repeated *i.p.* administration of norNOHA and the changes in plasma amino acid concentrations. No significant accumulation of norNOHA in the plasma occurred during repeated *i.p.* injections at the dose of 30 mg/kg once daily for 5 days. Only small increases were found between the first and fifth applications in the AUC and C_{max} values. Due to the inhibitory effect of norNOHA the shift was observed from arginine utilization: the ratio of citrulline/ornithine in the plasma augmented by 45 % and that of citrulline/arginine by 25 %, respectively. Regardless of the dosing schedule, norNOHA caused no changes in plasma L-arginine. Following the fifth *i.p.* dose of norNOHA, plasma levels were elevated of glutamine and histidine v plazmě. Whether or not this finding indirectly signals inhibition of the liver Arg I and decreased amonia detoxification in the urea cycle should be further explored.