Alterations in L-Arginine Metabolism After Lung Transplantation

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Abstract: Since the discovery of nitric oxide (NO) in biological systems more than 20 years ago, it became widely accepted that endogenous NO plays a key role in the regulation of a variety of physiological processes. NO is involved in reperfusion injury and chronic rejection after solid organ transplantation. Arginase is an enzyme that competes with NO synthases for the common substrate L-arginine. Increased arginase activity alters L-arginine metabolism and reduces substrate availability for NO synthases, and thereby contributes to organ dysfunction following transplantation. NO deficiency after lung transplantation impacts on perfusion and ventilation of the donor organ. L-ornithine, the product of arginase activity, is precursor for polyamine and proline biosynthesis which are both involved in airway remodeling. The purpose of this review is to summarize the current knowledge on the role of alterations in the L-arginine metabolism in lung transplantation.

Keywords: Arginase, l-arginine, lung transplantation, nitric oxide, solid organ transplantation.

NO/L-ARGININE METABOLISM

Nitric oxide (NO) is synthesized by three NO synthase (NOS) isoforms, neuronal (nNOS or NOS1), endothelial (eNOS or NOS3), and inducible NOS (iNOS or NOS2). The isoforms are found in a variety of different cell types, and all three are expressed constitutively in normal airway epithelium. NOS1 and NOS3 are regulated by the intracellular calcium/calmodulin level and are also often referred to as constitutive NOS (cNOS). Expression of NOS2 is calcium independent and responds to proinflammatory cytokines, such as interleukin 1 (IL-1), IL-6, interferon γ, and tumor necrosis factor α (TNF-α) directly and via nuclear factor-xB (NFxB) [1-3]. Epithelial NOS2 is thought to be the major source of increased fractional NO in exhaled air (FeNO) in inflammatory conditions such as asthma and FeNO can therefore be used as a marker of airway inflammation in asthma [4].

NO is a neurotransmitter, regulates smooth muscle tone and acts as a vasodilator, increases blood flow and may have effects on platelet function. In addition, NO reduces inflammation by antagonizing lymphocyte and neutrophile activation and inhibition of adhesion of neutrophils. NO prevents apoptosis and neutralizes free radical injury [5-9]. Interestingly, iNOS, which produces NO in large amounts after stimulation, in the absence of substrate is also capable of superoxide anion production and subsequently formation of the toxic radical peroxynitrite [10].

NOSs produce citrulline and NO and compete with arginase for L-arginine as substrate. L-arginine is a compound of normal food but also of immunonutrients. It may reduce catabolism (protein breakdown) by compensating for increased arginine need, correct for endothelial dysfunction by providing substrate for NOS3 and may improve immune response. L-arginine was found to augment bacterial phagocytosis in human polymorphonuclear leukocytes (PMN) [11]. The product of arginase activity is ornithine. Ornithine is metabolized by the enzyme ornithine aminotransferase (OAT) to form proline, the precursor of collagen formation, but also by ornithine decarboxylase (ODC) to form polyamines (putrescine, cadaverine, spermidine, and spermine), which are involved in cell proliferation and repair. Polyamines are also capable of protecting against free radicals and against DNA strand breaks due to reactive oxygen species. In addition, polyamines inhibit locomotion of human neutrophils [12], and also play a crucial role in the control of apoptosis [13]. Interconversion of polyamines on the other hand results in production of cytotoxic compounds such as hydrogen peroxide and aldehydes [14]. Another intermediate in polyamine biosynthesis is agmatine, which is the product of arginine decarboxylase. Agmatine is a putative neurotransmitter that binds to α2-adrenergic receptor and imidazole binding sites, and blocks NMDA receptors and other cation ligand-gated channels. Agmatine, which may also inhibit NOS, is inactivated by the enzyme agmatinase. Another naturally occurring inhibitor of NOS is asymmetric dimethylarginine (ADMA), a metabolic by-product of protein methylation and degradation. The elimination of ADMA occurs through metabolism by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) and urine excretion.

L-ARGININE/NO PATHWAY AND SOLID ORGAN TRANSPLANTATION

Alterations in the L-arginine/nitric oxide (L-arg/NO) metabolic pathway play a role in a variety of problems after solid organ transplantation. However, findings are complex and often inconsistent. Both beneficial and detrimental effects of NO are described in the literature, dependent on fac-
tors such as the time course after transplantation and differ between ischemia/reperfusion injury, primary graft dysfunction, as well as acute and chronic rejection. Furthermore, alterations and consequences often differ between organs, thus interpretation of findings from one form of transplantation cannot be generalized to others. Below, we give a short summary of published findings on alterations of the L-arg/NO pathway in solid organ transplantations other than lung, before focusing on lung transplantation.

Kidney

In chronic kidney disease, there is considerable evidence that total systemic NO levels are decreased due to impaired endothelial and renal NO production. Mechanisms involved include substrate limitation for NOS due to decreased renal synthesis of L-arginine, substrate consumption by upregulated arginase [15], and decreased L-arginine delivery into cells, NOS inhibition by increased ADMA levels secondary to reduced DDAH activity, and reduced expression or activity of renal eNOS. Evidence from animal studies suggest that experimentally induced chronic NOS inhibition causes systemic and glomerular hypertension, glomerular ischemia, glomerulosclerosis, tubulointerstitial injury and proteinuria [16,17]. Observations from diverse models of renal failure showed that L-arginine has nephroprotective effects. Schramm et al could demonstrate that in experimental acute renal failure, decreased renal plasma flow (RPF) and glomerular filtration rate (GFR) were associated with reduced tissue L-arginine levels, endothelial eNOS expression, NO formation and NO3 and NO2 excretion. The reduction in RPF, GFR and NO2 excretion were reversed upon administration of exogenous L-arginine [10]. In transplanted kidney, there seems to be a dual role of L-arginine: mediating renal protection as well as renal injury. In the early phase beneficial effects of L-arginine supplementation appear to outweigh. In an allogeneic renal transplant model in rats, treatment with L-arginine restored renal graft function in recipients with moderate vascular and interstitial rejection. Furthermore, L-arginine significantly reduced vascular occlusion by reducing inflammation, endothelial disruption and thrombosis, and decreased tubulitis, interstitial injury and macrophage infiltration [8]. L-arginine enriched preservation solution has also been shown to protect against ischemia/reperfusion injury when administered before the occurrence of renal ischemia [18], similar to oral L-arginine supplementation [19]. In human kidney transplant patients receiving organs after short cold ischemia time and from younger donors, that is those with a higher likelihood of functional endothelium, early administration of L-arginine improved renal function [10]. Beneficial effects of L-arginine might include modulation of NO production, enzymatic conversion into agmatine and stimulation of glucagon secretion, which both increase GFR [3].

Conversely, NO can promote renal rejection and therefore, L-arginine supplementation might be harmful if it enhances iNOS activity. In a model of acute rejection in allo- genic renal transplantation in rats, improved renal hemodynamics (increased GFR and reduced vascular resistance) were found after specific iNOS inhibition for seven days. Additionally, reduced tubulointerstitial macrophage influx and injury were observed in these animals [20]. Unspecific inhibition of NOS however, led to a significant increase in vascular and tubulointerstitial injury in the same model [21]. This might indicate that deleterious effects of loss of NO production from constitutive NOS outweigh the beneficial effects of iNOS inhibition. Furthermore, it is suggested that deleterious effects of the large amounts of NO produced by iNOS in invasive cells are more important than the potentially beneficial effects of NO produced by iNOS in resident cells [3].

Liver

There is accumulating evidence the L-arg/NO pathway is altered in liver diseases. Elevated circulating and excretory levels of NO2 and NO3 were found in patients with chronic liver disease and cirrhosis. In patients with chronic hepatic failure concentrations of the endogenous NOS inhibitor ADMA were found to be increased. Furthermore, elevated excretion rates of dimethylamine (DMA), the enzymatic hydrolysis product of ADMA, have been found in patients with end-stage liver disease [16].

Arginase 1 in liver is primarily found in the cytosol of parenchymal cells. With any traumatic event, including liver transplantation, arginase is released into the bloodstream and acts to deplete circulating L-arginine while increasing ornithine levels. In human orthotopic liver transplantation (OLT) higher than normal plasma arginase was found before transplantation. Arginase in these patients peaked at day one post transplantation [22]. Becker and coworkers investigated a wide spectrum of biochemical parameters with indicator function of the L-arg/NO pathway during and after OLT in humans. No significant change in nitrite plasma concentrations was found from pre- to four hours post transplantation while plasma nitrate concentrations fell significantly during that period. ADMA was elevated before transplant, showed an increase during the unhepatic period and fell after reperfusion to an almost normal level four hours after transplant. L-arginine did not differ pre-operatively when comparing end-stage liver disease patients and healthy controls, but fell dramatically 10 min after transplant, while L-ornithine, the product of arginase activity, increased [16].

Conflicting results were reported from interventional studies. In general, beneficial effects of L-arginine supplementation before and/or during and/or after liver transplantation were observed with respect to ischemia/reperfusion injury (I/R injury). Graft function seemed improved as liver enzyme release decreased [7, 23-25], hepatic microcirculation improved [24,26,27] and the number of adherent leukocytes in sinusoids and venules decreased in animal experiments [26]. Shimamura et al. described attenuated neutrophil infiltration following L-arginine supplementation before ischemia and during reperfusion in a model of temporary total hepatic vascular exclusion in dogs [24]. In contrast, in the late phase of liver reperfusion Ohmori et al. observed detrimental effects of L-arginine supplementation resulting in an increased level of circulating transaminases [27]. An explanation of these observations might be, that in the late reperfusion period L-arginine supplementation results in the production of large amounts of NO, which might be injurious because of a conversion to toxic compounds such as peroxynitrite.

Prevention of systemic L-arginine depletion after liver transplantation through the release of arginase 1 can be
achieved by arginase inhibition. The administration of $N$^\text{\text beta}-hydroxy-nor-L-arginine (nor-NOHA), a naturally occurring arginase inhibitor but also a direct substrate for NOS, improved liver I/R injury in a rat model of liver transplantation. Nor-NOHA resulted in a blunted decrease in serum arginase activity, preserved serum arginine levels and in markedly improved liver histology (degree of necrosis) [6]. In a further investigation by the same group [28], inhibition of arginase by nor-NOHA in a mouse model of warm I/R injury resulted in reversed arginine depletion while serum NO and circulating citrulline increased. Furthermore, protection from I/R-induced damage was observed (decrease in serum ALT, significantly less hepatocellular necrosis in liver tissue), which was associated with lower hepatic TNF, IL-6 and iNOS mRNA levels. Interestingly, FK409, a NO donor given in an animal model of liver I/R injury resulted in beneficial effects comparable to L-arginine supplementation [24,27,28].

To further characterize the cytoprotective and/or cytotoxic effects of NO during I/R, several investigators studied the effect of NOS inhibition. Unspecific NOS inhibition can be achieved by administration of inhibitors such as $N$^\text{\text beta}-nitro-L-arginine (L-NNA), $N$^\text{\text beta}-nitro-L-arginine methyl ester (L-NAME), which requires hydrolysis of the methyl ester by cellular esterases to become the fully functional inhibitor L-NNA, or by $N$^\text{\text gamma}-monomethyl-L-arginine (L-NMMA). Observations after unspecific NOS inhibition are consistent with negative effects with regard to I/R injury: increased liver enzymes, necrotic and apoptotic cell death, neutrophil infiltration and leukocyte adherence as well as reduced sinusoidal blood flow were described [7,23,25,26]. Specific iNOS inhibition alone (e.g. by administration of aminoguanidine (AG) or L-N6-(1-iminoethyl)lysine (L-NIL)), which is inhibited by nor-NOHA in a mouse model of warm I/R injury resulted in beneficial effects comparable to L-arginine supplementation [32,34].

Beneficial effects of NO have been suggested repeatedly in chronic rejection after cardiac transplantation. The mechanism of protective action with limited chronic transplantation-induced atherosclerosis and vasculopathy has been explained by the ability of NO to limit adhesion of platelets and leukocytes to vascular endothelium and to induce apoptosis of macrophages and proliferating vascular smooth muscle cells [51-53].

**LUNG**

**Exhaled Nitric Oxide**

Pulmonary NO formation can be assessed directly by measuring the fraction of NO in exhaled air (FeNO). FeNO is a non-invasive marker of airway inflammation and is altered in airway diseases such as asthma, COPD, cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) [4,54-59]. Marczin and colleagues [60] reported a substantially diminished NO production by cadaver lung allografts during the perioperative period. The few studies that were done in lung transplant patients with regards to the role of FeNO in detecting acute rejection (AR), infection or bronchiolitis obliterans syndrome (BOS) revealed inconsistent results. A longitudinal study from Toronto that was performed over a 12-month period in 108 lung transplant recipients suggested that FeNO was significantly increased during episodes of acute rejection, while FeNO was not elevated in BOS or pulmonary infection [61]. A retrospective analysis of bronchoscopic findings and concurrent FeNO in a limited number of patients suggested that changes in FeNO did not correlate with histological findings (normal, acute rejection grade I, nonspecific inflammatory change) or with a positive airway microbiology culture [61]. However, increased FeNO in acute rejection could not be confirmed in other clinical studies [62,63]. In contrast, increased FeNO was described in patients with chronic rejection/BOS [62-66]. Verleden and his group found increased FeNO in all patients with clinically diagnosed BOS [64], but several others reported raised FeNO only in unstable BOS patients [65] i.e., those with recent clinical deteriorations [62,67,68] or in early stages of BOS [63,66]. Increased FeNO was also described in lung transplant recipients with respiratory infections [62,63].

**Nitric Oxide Metabolites**

Only few studies were performed to measure stable NO metabolites in lung transplant recipients. De Andrade and
colleges described significantly increased total nitrate levels in bronchoalveolar lavage fluid (BALF) and in serum of lung transplant patients compared to controls [69]. However, in this study no information was given on the clinical status of the patients with respect to infection, or acute or chronic rejection. Reid et al. confirmed the finding of increased nitrite levels, however, when separating stable patients (including those with no more than A1 grading for acute rejection on histology) and BOS patients, only patients with BOS showed significantly increased levels of nitrite in BALF [70]. Increased levels of circulating nitrates were observed in animal models of acute cellular rejection [71,72]. Taken together, these data may suggest that NO production is increased in the pulmonary endothelium in acute rejection but not in the airways in chronic rejection/BOS. However, comprehensive data on NO metabolites in both serum and BALF comparing stable lung transplant recipients with patients experiencing acute or chronic rejection are lacking.

Nitric Oxide Synthases

Several events during the transplant process may influence the L-arginine metabolism in the donor lung. While hypothermia is essential for organ storage it is also associated with oxidative stress, intracellular calcium overload and induction of cell death which may induce the release of proinflammatory mediators known to induce NOS. The absence of vascular flow during ischemia stimulates membrane depolarization of endothelial cells with direct activation of calcium/calmodulin-dependent NOS and activation of nuclear factor-κB (NFκB), a stimulator of NOS [73]. To study alterations in NOS expression and NOS activity, Liu and coworkers used ex vivo and in vivo models of lung injury related to preservation and reperfusion in rats [74]. To avoid allograft-related immune response isograft transplantations (single lung) were performed. In the ex vivo model, the authors could demonstrate an increase in iNOS expression 2h after reperfusion, but a decrease of eNOS expression after the same time. Interestingly, in the in vivo model no changes were found in the recipients’ native lungs, supporting the notion that the increase in iNOS observed in the transplanted lung was a result of a specific ischemia-reperfusion related response rather than a generalized systemic inflammatory response. Of note, despite the increased level of NOS protein levels, total NOS activity, measured by the conversion of L-arginine to L-citrulline in vitro, remained at very low levels [74].

In acute rejection, alterations in NOS expression and/or activity were observed in several studies. Worrall and colleagues demonstrated increased lung NOS expression and activity as well as increased serum nitrite/nitrate levels in a rat model of acute allograft rejection [72]. Similarly, in a model of acute rejection in dogs, iNOS expression in lung parenchyma was increased as were plasma levels of NO metabolites, while lung eNOS expression was decreased [75]. Elevated iNOS mRNA transcription levels were also found in airway cells obtained from human allografts by BAL, however, an increase in iNOS was not predictive for acute rejection; a significant increase was only detected in cases of bacterial infection [76].

Expression of iNOS is also increased in obliterative bronchiolitis (OB) and its clinical equivalent BOS. In an animal model of OB, airway epithelial cell expression of iNOS increased in parallel to epithelial damage. Furthermore, fibroblasts expressed iNOS at all stages of obliterative airway disease, more intense in the early phase following allograft implantation than in the late phase. In the early phase iNOS-immunoreactive fibroblasts could be seen in the adventitial and submucosal zones and, with the onset of graft obliteration, also within the tracheal lumen. With further progression of obliteration down-regulation of iNOS immunoreactivity in fibroblasts occurred, which corresponded with the previously described raised FeNO in early but not in advanced stages of BOS [63,66]. Moreover, the intensity of immunoreactivity for iNOS corresponded to that for nitrotyrosine, a marker of formation of the reactive oxidant peroxynitrite and therefore of NO-mediated cytotoxicity [77]. This indicates that increased NO formation in airway obliteration following transplantation leads to destruction of epithelium and stimulation of fibroblast activity. The detrimental effect of increased iNOS expression together with increased NO formation was confirmed in a model of OB in mice [78]. In this study a significant reduction in local expression of proinflammatory chemokines and cytokines, graft T cell recruitment and apoptosis, as well as luminal obliteration were observed in wild-type allografts of iNOS (-/-) recipients. Of interest, recipient eNOS deficiency however, suppressed neither described inflammatory reaction nor airway occlusion. Furthermore, no beneficial effect could be observed for iNOS (-/-) allografts of iNOS (+/+), arginase activity in transplant recipients presenting with OB/BOS [62,79], which corresponded to increased nitrotyrosine [79] and FeNO [62].

Arginase

Although an increasing number of publications suggest that arginase is important in different lung diseases, only very little is known about alterations in the L-arginine-/arginase metabolic pathway after lung transplantation. In a rat model, total arginase activity was found to be increased in acute lung allograft rejection, as was the expression of both arginase 1 and arginase 2. Arginase activity in transplanted lungs showed a statistically significant correlation with peak airway pressure and collagen deposition. Furthermore, treatment with Pirfenidone, an investigational antifibrotic agent, reduced lung arginase expression, arginase activity and peak airway pressure in this rat model of acute rejection after lung transplantation, possibly through suppression of endogenous transforming growth factor β (TGF-β) [80]. These data suggest a functional relevance of increased arginase in acute lung allograft rejection.

INTERVENTIONAL STUDIES

Several strategies have been developed to modulate NO formation during lung transplantation. These strategies have been applied to the donor and/or to the recipient and have targeted almost each step of the L-arginine/NO-pathway:

Supplementation of L-Arginine

As in other solid organ transplantation the administration of L-arginine during and/or after the ischemia-reperfusion
period was expected to compensate for the fall in endogenous NO and to ameliorate injury of the transplanted lung. While in some studies beneficial effects of L-arginine supplementation were described in animal models i.e. prevention of pulmonary endothelial damage after reperfusion [81,82] or improved oxygenation [83], others could not observe effects of L-arginine on pulmonary hemodynamics, gas exchange, or leukocyte sequestration of the transplanted lung [84].

Inhaled Nitric Oxide

Several studies were performed in order to prevent primary graft dysfunction (PGD) with inhaled NO. In an experimental study in rats NO-inhalation seemed to be beneficial when started during reperfusion [85]. A reduction in pulmonary vascular resistance, a decrease in myeloperoxidase activity and reduction of endothelial permeability was described. Another study in humans where inhaled NO was combined with administration of exogenous surfactant showed improved arterial oxygenation and reduced neutrophil extravasation [86]. However, in a prospective, randomized, blinded clinical trial evaluating the prophylactic administration of inhaled NO in 84 patients undergoing lung transplantation [87], there was no difference in incidence of PGD when inhaled NO was started 10 min after reperfusion. When looking at lung tissue samples in a subset of patient, NO inhalation was found to increase cNOS, but not iNOS expression. However, the total NOS activity remained at low levels [88]. In other prospective studies inhaled NO given at reperfusion did not prevent or reduce the incidence of PGD when compared with historic controls [89], or showed no benefit of inhaled NO administered at the onset of reperfusion on incidence of PGD grade 3, gas exchange, neutrophil sequestration, or BAL concentration of proinflammatory cytokines [90].

However, inhaled NO has been used in the treatment of PGD in lung transplantation based on its ability to reduce pulmonary artery pressure without affecting systemic pressures, combined with improvement in ventilation perfusion mismatch. Several case series have suggested that administration of NO can result in improved clinical outcome [91-93], while others reported no therapeutic effect of inhaled NO on PGD [94]. To date, there is no prospective, randomized clinical trial comparing NO to placebo. Of interest, Cornfield and coworkers studied the safety of NO inhalation and found no significant side effects but a significant decrease of the occurrence of acute allograft rejection during the first 4 weeks after transplantation [95].

NO Donors

Other strategies of NO supplementation, indirectly via infusion of a NO donor, such as FK409 [96,97], nitroprusside [98-100] or nitroglycerin [78,101,102] have shown to be effective in experimental settings. However, no study so far was conducted in humans.

Changing NOS Activity

Another strategy has been directed at increasing NOS activity by transfecting the donor lung with an adenovirus containing endothelial NOS before organ retrieval. In an experiment performed by Suda and colleagues the focus of interest was in I/R injury after lung transplantation. This group reported ameliorated I/R injury as manifested by significantly improved oxygenation and decreased neutrophil sequestration in transplanted lung isografts [103]. Others focused on acute rejection after allogenic lung transplantation without immunosuppression in rats [104]. This study reported a functionally active transgene product and increased NO production in pulmonary allografts, which did however not affect the grade of histologically identified acute rejection [104]. Tetrahydrobiopterin (BH4), a cofactor of NOS was administered to increase NOS activity and to reduce I/R-injury in pigs. In his study a significant reduction of extravascular lung water and reduced lipid peroxidation was found one hour after transplantation in animals receiving BH4 compared to controls [105]. In a second study from the same group, prolonged preservation time of 30 hours could be reached by adding 8-Br-cGMP, a second messenger of NO, to the flush solution and continuously infusing BH4 to the recipient during 5 hours after transplantation. While no animal survived the 12 hour assessment in the control group, in the treatment group two of five animals survived with slightly deteriorated gas exchange and three with normal arterial oxygenation [106].

In contrast to other solid organ transplantation studies investigating the impact of NOS inhibition on the course after lung transplantation are rare. Shiraishi et al. reported that NO production during acute lung allograft rejection was effectively inhibited by the administration of aminoguanidine (AG), a selective iNOS inhibitor, in a rat lung allotransplant model [107]. Histologically the degree of rejection was significantly suppressed by AG in the early phase of rejection compared with the control group. These data suggest a deleterious effect of NO in the process of allograft rejection. Other authors confirmed this beneficial effect of AG on the course of acute rejection, reporting improvement in gas exchange and suppression of histological changes by administration of AG [108], and reduction of the allogeneic response when combined with low doses of cyclosporine compared to low doses of cyclosporine alone [109]. In a study looking at long-term effect of NOS inhibition by AG resulted in prolonged allograft survival [110].

CONCLUSIONS

Alterations in the L-arginine/NO metabolism occur after solid organ transplantation and contribute to short and long-term outcome of lung transplant recipients. Further studies are needed to investigate the therapeutic potential of drugs aiming to modulate the availability of L-arginine for nitric oxide synthases and arginase after lung transplantation.

ABBREVIATIONS

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<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACR</td>
<td>Acute cellular rejection</td>
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<td>ADMA</td>
<td>Asymmetric dimethylarginine</td>
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<td>AG</td>
<td>Aminoguanidine</td>
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<td>BALF</td>
<td>Bronchoalveolar lavage fluid</td>
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<td>BOS</td>
<td>Bronchiolitis obliterans syndrome</td>
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<td>CF</td>
<td>Cystic fibrosis</td>
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<td>cNOS</td>
<td>Constitutive nitric oxide synthase</td>
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<td>DDAH</td>
<td>Dimethylarginine dimethylaminohydrolase</td>
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