

Research Profile



Anibh M. Das

- University:** M.D. at Göttingen University (Germany), 1986
- Thesis:** Ph.D. at Göttingen University, Department of systemic physiology: “Effect of oleic- and palmitic acid on myocardium and heart mitochondria under low-flow anoxia”, 1988 (summa cum laude)
- Scholarship:** 1987- 1988 Max-Planck Institute for experimental medicine. Department of Physiology (Prof. Piiper)
- Postdoc:** 1988-1990 University of Oxford, Department of Biochemistry (Dr. D.A. Harris)
- Qualifications:** Paediatrician, 1999; PhD (‘Habilitation’) at Hannover Medical School 2001, Professor (Paediatrics) 2006
- Clinical work:** 1990-1996: Training in Paediatrics, Hannover Medical School (Germany)
1996-2000: Paediatrician, Department of Paediatrics, Hamburg University (Germany)
2000-present: Head of Paediatric Metabolic Medicine, Department of Paediatrics, Hannover Medical School

Current Research:

Our research projects focus on the impact of inborn errors of metabolism (IEM) on brain function. Thus, we hope to further the understanding of cerebral dysfunction in IEM. IEM can in principle be subdivided into the following 3 categories:

1) ‘Intoxication’ type:

In IEM, deficiency of an enzyme leads to the accumulation of the substrate which is normally degraded by this enzyme. The accumulating substrates are 'toxic' and lead to clinical symptoms.

An example for this type of IEM is *phenylketonuria* (PKU) which has an incidence of 1:7,500 newborns and leads to severe encephalopathy with profound mental retardation and seizures if not treated within the first days of life. Protein-restricted diet for life is the treatment of choice. Despite therapy compliance neurological development is not completely normal in all patients as judged by psychometric testing. In cooperation with the Department of Neuroradiology at Hannover Medical School we currently study young adults with early-treated PKU and try to correlate functional MRI- and spectroscopy-findings with metabolic and nutritional parameters in order to identify other prognostic parameters apart from phenylalanine levels in blood.

2) 'Storage' type:

In this type of IEM endogenous substrates accumulate in the cell due to an impairment of degradative pathways based either on compromised enzyme activity or transporter dysfunction.

For several of these disorders (e.g. M. Gaucher, M. Fabry, M. Hurler-Scheie) enzyme replacement therapy has been developed. As the enzymes cannot cross the blood-brain barrier, cerebral storage processes are not influenced by this therapeutic measure, leading to neurodegeneration, for example in M. Hurler (MPS I). Bone marrow transplantation is the method of choice in these patients. In cooperation with the Department of Paediatric Haemato-Oncology we look after children with M. Hurler who received bone marrow transplantation at our institution and follow their neurodevelopmental course.

Niemann-Pick Disease Type C (NPC) is another neurodegenerative disease caused by a defect in cholesterol transport. We plan to elucidate the pathophysiological processes leading to clinical symptoms in NPC by examining energy metabolism, protein trafficking and 'lipid rafts' in cooperation with the Department of Physiological chemistry of the Veterinary School in Hannover.

3) 'Energy depletion' type:

Energy metabolism is the main research focus of our group. Primary defects of energy metabolism cause multisystemic disease that can directly affect the brain. As brain biopsy is not possible in humans assays of energy metabolism in extracerebral tissues have to be extrapolated to the brain. We measure *mitochondrial respiratory chain* complexes I-V including active regulation of the ATPsynthase in skin fibroblasts and muscle biopsies from patients suspected to suffer from mitochondriopathies.

Secondary impairment of mitochondrial energy metabolism may play a role in the pathophysiology of lysosomal storage diseases. We have found compromised energy metabolism in cultured fibroblasts from patients with neuronal ceroid-lipofuscinosis (NCL) and M. Fabry. Lack of cellular energy may be responsible for abnormalities in protein and lipid trafficking which may result in altered membrane lipid composition and compromised function of 'lipid rafts' in the plasma membrane. Substrate reduction therapy as well as enzyme replacement therapy may reduce cellular dysfunction. Small molecules like N-butyl-deoxynojirimycin (Miglustat®) lead to substrate reduction in lysosomal storage diseases by inhibiting the synthesis of accumulating substances. At the same time they may act as chaperones, thus increasing residual activity of transporters/enzymes. As they can cross the blood-brain barrier they are a promising tool to reverse brain pathology. We shall study the effect of both substrate reduction and enzyme replacement/chaperones on secondary biochemical pathology in vitro.

Fatty acid oxidation defects (FAOD) do not directly affect neuronal cells as fatty acid oxidation does not play a major role in energy generation of the brain. However, especially in FAOD of long and medium chain fatty acids ‘toxic’ lipophilic substances are produced, particularly during metabolic crises. These may have a negative effect on neurons and other extracerebral cells of the body. We plan to study transport processes regulating in- and efflux of ‘toxic’ substances which may lead to the development of protective agents.

IEM of energy metabolism can also lead to *skeletal- and cardiomyopathy*. We are interested in diagnostic procedures of both FAOD and respiratory chain defects of muscle. Furthermore, energy depletion in vascular smooth muscle cells can lead to compromised function of blood vessels (‘latch’ state). We study this in diseases with primary (MELAS) and secondary (M. Fabry) defects in oxidative phosphorylation and other diseases with compromised vascular function (M. Schimke). As a further regulatory element of vascular tonus NO-metabolism is assessed in these disorders.

As Hannover Medical School focuses on organ transplantation we see many patients with liver and kidney failure who present with secondary acute encephalopathy.

Currently, we study patients suffering from the haemolytic-uraemic syndrome (HUS) who develop neurological complications, using imaging techniques (MRI and spectroscopy), electrophysiology and psychometry.

Those patients, who have to undergo liver- or kidney transplantation, receive long-term immunosuppression. About a third of these patients develop neurological problems. Some immunosuppressants like ciclosporine A are known to interfere with mitochondrial function. Currently, we do a prospective clinical survey of transplanted paediatric patients and try to correlate clinical symptoms with mitochondrial function in cultured fibroblasts of these patients.

Future projects and goals:

As mentioned above, studies on secondary defects of energy metabolism and abnormalities in membrane function shall be extended to other lysosomal storage diseases. These abnormalities may help to understand brain dysfunction in lysosomal storage diseases.

‘Ketogenic diet’ is an established therapeutic option in ‘therapy-resistant’ epilepsy. However, the biochemical mechanism leading to the antiepileptic effect is unknown. We plan to investigate alterations of biochemical pathways under ‘ketogenic diet’.

We plan to identify new regulatory elements of energy metabolism which may be compromised in IEM.

Abnormalities (‘immaturity’) in metabolic pathways may contribute to organ dysfunction, especially of the brain. This issue shall be addressed by examining metabolic pathways in HUVEC and fibroblasts from premature babies.

Selected publications:

1. Das AM, Naim HY. Invited review: Biochemical basis of Fabry disease with emphasis on mitochondrial function and lipid trafficking. *Adv Clin Chem* 49: 57-71
2. Illsinger S, Lücke T, Peter M, Ruiter JP, Wanders RJ, Deschauer M, Handig I, Wuyts W, Das AM (2008) Carnitine-palmitoyltransferase 2 deficiency: Novel mutations and relevance of newborn screening. *Am J Med Genet A* Oct 16 [Epub ahead of print]

3. Das AM, Illsinger S, Lücke T, Hartmann H, Ruiter JPN, Steuerwald U, Waterham HR, Duran M, Wanders RJA (2006) Isolated mitochondrial long chain keto-acyl-CoA-thiolase deficiency due to mutations in the HADHB gene. Clin Chem, 52: 530-534. Lücke T, Höppner W, Schmidt E, Illsinger S, Das AM (2004) Fabry Disease: Reduced activities of respiratory chain enzymes with decreased levels of energy-rich phosphates in fibroblasts. Mol Genet Metab, 82:93-97.
4. Das AM (2003) Review: Regulation of the mitochondrial ATP-synthase in health and disease. Molec Genet Metab, 79: 71-82.
5. Das AM, von Harlem R, Feist M, Lücke T, Kohlschütter A (2001) Altered levels of high-energy phosphate compounds in fibroblasts from different forms of neuronal ceroid lipofuscinoses: further evidence for mitochondrial involvement. Eur J Paediatr Neurol 5, Suppl. A: 143-146.

Group structure:

Group leader: Anibh Das

Academic members: Hans Hartmann, Thomas Lücke, Sabine Illsinger, Nils Janzen

Postgraduate students: Katia Maalouf, Kristin Goedecke

Technicians: Jolanthe Bednarczyk, Karl Heinz Schmidt

Specialist Dietician: Uta Meyer

Contact:

Prof. Dr. Anibh Martin Das

Medizinische Hochschule Hannover,

Klinik für Pädiatrische Nieren-, Leber- und Stoffwechselerkrankungen

Carl Neuberg Str. 1

D- 30625 Hannover

Phone: 0511 532 3220 (switchboard)

Fax: 0511 532 8073

Email: das.anibh@mh-hannover.de