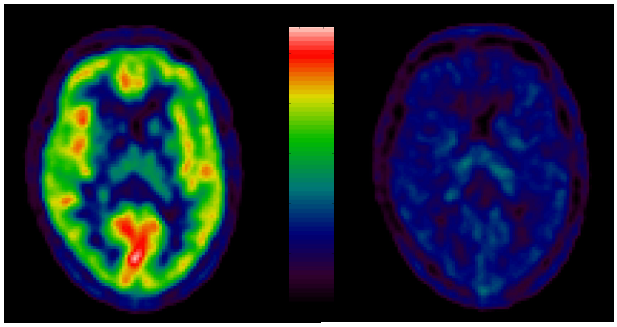
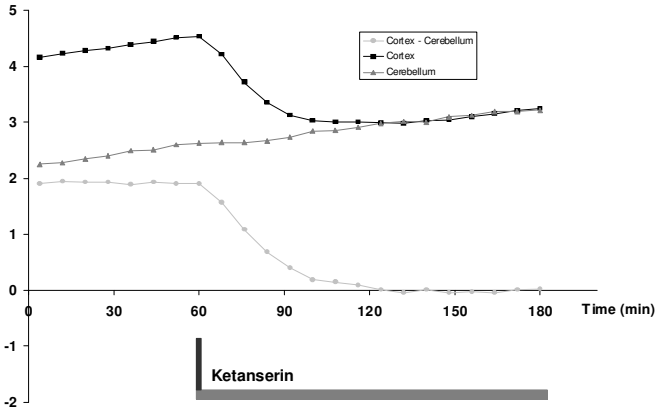
Annual Report 2003

Neurobiology Research Unit





Dept. Neurology, Neuroscience Centre
Rigshospitalet
The Health Science Faculty
Copenhagen University

www.nru.dk

Front page:
Ketanserin is structurally closely related to [^{18}F]altanserin. Sixty minutes after [^{18}F]altanserin steady-state was attained in brain and plasma, saturating doses of cold ketanserin were administrated and it was found that the cortical concentration of [^{18}F]altanserin decreased uniformly to the level of cerebellum and no change in the cerebellar time-activity curve was found. Thus, for [^{18}F]altanserin there is no detectable specific cerebellar binding to 5-HT_{2A} receptors, and cerebellum may be used as a reference region for quantification of [^{18}F]altanserin binding to the 5-HT_{2A} receptors. From Pinborg et al, 2003.

Preface

We are happy to present to you the annual report that provides an overview of the scientific activities that took place within the Neurobiology Research Unit (NRU) in 2003.

In April, chief consultant Steen G. Hasselbalch defended his doctoral thesis 'Quantitation of brain metabolism in humans using PET-FDG: levels and limitations'. This thesis builds on seven methodologically elegant and well composited papers. They will undoubtedly become the main papers when considering the correction factor in the conversion between fluorodeoxy-glucose measurements with PET and glucose metabolism in the brain.

In addition, two PhD-theses were defended: In January, Betina Elfving defended her thesis that focuses on serotonin transporter tracers, with particular emphasis on the failure of ^{11}C-citalopram to work as a PET-tracer and in May, Jacob Madsen defended his thesis on development of radiotracers for PET-measurements of serotonin transporter binding in humans.

At NRU, we are in the fortunate situation that a large fraction of our technical staff has had a long-standing employment and commitment for research. It was an honour for NRU that our chief technologist, Gerda Thomsen, in addition to her job as the daily leader of the SPECT-laboratory successfully completed her exams in 'The Leadership Development Program of Rigshospitalet'.

In February, Professor Olaf Paulson was awarded the Lundbeck prize for his life-long achievements within brain research and this was celebrated at a well-visited reception at Rigshospitalet. Olaf Paulson gave a presentation of his work particularly focussing on cerebral blood flow autoregulation and ended with an overview of brain mapping.

The University of Copenhagen has allocated the theme 'Body and Mind' (Krop og Bevidsthed) as one of their priority areas within the University. This consortium which is based on a cross-disciplinary collaboration between several faculties at the University was inaugurated in 2003. We expect that for NRU this collaboration will create many new interesting research projects.

As in the previous annual reports, the NRU publications are described in separate sections within this report. We hope that you will enjoy reading the Year 2003 Annual Report!

Olaf B. Paulson *Claus Svarer* *Gitte Moos Knudsen*

Table of Contents

1. Research Facilities

Since June 1996 the Neurobiology Research Unit has been located at Juliane Maries Vej 24 in an old villa named Building 92 at the Rigshospitalet campus. In this house NRU has offices and facilities for data analysis.

The SPECT laboratory of NRU is located at the Department of Neurology on the 8th floor in the main complex of Rigshospitalet. The laboratory includes a room for the Philips IRIX SPECT scanner, a type B approved isotope laboratory, and a small office. Further office and laboratory facilities are shared with other employees at the department.

The NRU experimental laboratory resides in Building 93, Juliane Maries Vej 20, just opposite Building 92. The ground floor of Building 93 is shared with the Neuro-immunology Laboratory and with the Cardiovascular Laboratory. Four laboratory rooms are allocated for NRU, and it shares another three rooms and two offices with the above mentioned research groups.

NRU conducts its PET research activities in close collaboration with the Department of Clinical Physiology/Nuclear Medicine, and has access to the three PET scanners in the PET Unit in the Finsen Building at Rigshospitalet. NRU has a close collaboration with the Department of Clinical Physiology/Nuclear Medicine in the research-planning and developmental activities.

2. Objectives, Organization and Staff

NRU has its main interest within molecular imaging, with particular focus on neuroreceptor imaging. Traditionally, the research unit has also been involved with studies of cerebral blood flow and metabolism and functional brain mapping. As for the latter, most of these studies are now carried out at the Danish Research Centre for Magnetic Resonance (DRCMR), Hvidovre University Hospital. Finally, image analysis and tracer kinetics remains issues that receive high attention within the unit.

The research group is chaired by Professor Olaf B. Paulson, who since 1995 also has chaired the DRCMR at Hvidovre Hospital. Research Professor, Consultant Gitte Moos Knudsen, DMSc, and Chief Engineer Claus Svarer, PhD, take part in chairing the research group. Gitte Moos Knudsen chairs the experimental laboratory in Building 93 and the SPECT laboratory. The Chief Technologist is Gerda Thomsen.

In 2003 the research staff consisted of:

Senior Researchers:
Susana Aznar, Biologist, PhD
Betina Elfving, Pharmacologist, PhD
Christian Gerlach, Psychologist, PhD*
Steen Hasselbalch, MD, DMSc (½ time)
Gitte Moos Knudsen, Professor, MD, DMSc
Jacob Madsen, Chemist, PhD*
Olaf B. Paulson, Professor, MD, DMSc
Claus Svarer, Engineer, PhD

PhD-students:
Karen Husted Adams, Pharmacologist
Daniela Balslev, MD
Steven Haugbøl, MD
Esben Høgh-Rasmussen, Engineer
Lars Hageman Pinborg, MD
Kristin Scheuer, MD
Kåre Søndergaard, Chemist*

Junior Researchers:
Robin de Nijs, Physicist*
Tim Dyrby, Engineer
Vibe Gedsø Frøkjær, MD
Viktorija Kostova, Human Biologist
Matthew Liptrot, Engineer
Birgitte Rahbek, Human Biologist
Thomas Rask, Engineer Student

Associated Researchers:
Morten Blinkenberg, MD, PhD
Ian Law, MD, PhD

Students:
Haroon Arfan, medical student
Dorte Brask, medical student
Heidi Kristiansen, biology student
Karine Madsen, medical student
Sofie Hansen, medical student
Kirsten Nielsen, medical student
Mikael Johansen, engineer student
Pernille Opstrup, medical student
Anders Pryds, medical student*
Jan Tønnesen, biology student
Morten Ziebell, medical student

Technologists:
Inge Møller
Anja Pedersen
Glenna Skouboe
Karin Stahr
Gerda Thomsen

Research Assistants:
Allan Frank
Nikolaj Hjortholm
Simon Krabbe
Lene Rottensten
Michael Twardak

Secretaries:
Pia Farup
Dorthe Givard

* shared with another research group

Guest Researchers:
Per Hartvig, Adj. Professor, Department of Analytical Pharmaceutical Chemistry, University of Uppsala, Sweden
Mads Rasmussen, MD, PhD-student, Department of Neuroanaesthesiology, Aarhus Kommunehospital

3. Collaborators in 2003

Copenhagen Brain Research Center

www.cbrc.dk

The center was inaugurated in April 2002 based on already existing collaboration between the involved partners. It consists of a multidisciplinary collaboration among institutes and departments in the Copenhagen area working with brain related research. These institutions include:

- Department of Medical Chemistry, The Danish University of Pharmaceutical Sciences
- H. Lundbeck A/S, Copenhagen
- Danish Research Center for Magnetic Resonance, Hvidovre Hospital
- The PET and Cyclotron Unit, Rigshospitalet
- Informatics and Mathematical Modelling, Technical University of Denmark
- Neurobiology Research Unit, Rigshospitalet
- Department of Psychology, Faculty of Humanities, University of Copenhagen

The center currently has 5 PhD-students engaged with supervisors from at least two different partners.

Additional departments within Rigshospitalet

Department of Cardiology

Department of Hepatology

Department of Infectious Diseases

Department of Neuroanesthesiology

Department of Neurosurgery

Department of Pediatrics

Department of Psychiatry

Additional research groups within H:S (Copenhagen Hospital Corporation)

Department of Clinical Physiology, Bispebjerg Hospital

Department of Neurology, Bispebjerg Hospital

EU 5th Framework Programs

Neuroreceptor Changes in Mild Cognitive Impairment (NCI-MCI), QLRT-2000-00502

Department of Geriatrics, Huddinge Universitetssjukhus, Sweden

PET Centre, Free University Hospital, Amsterdam, The Netherlands

PET Center, Karolinska Institutet, Stockholm, Sweden

Uppsala University PET Centre, Uppsala, Sweden

University 'Federico II', Napoli, Italy

Enhancement of Clinical Value of Functional Imaging Through Automated Removal of Partial Volume Effect (PVEOut), QLRT-1999-30594

Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, Sweden

Electric Engineering Laboratories, University of Kent at Canterbury, United Kingdom

Inserm U320, Caen, France

National Council for Research (CNR), Centre for Nuclear Medicine, Napoli, Italy

PET Centre, Debrecen, Hungary

RASNA Imaging Systems, Firenze, Italy

Development of New Radiotracers for the in-vivo Assessment of Biological Functions and Drug Interactions (COST).

Collaborators within COST, workgroup 1: Radioligands for Brain Receptors.

PET-centres in Orsay, Villigen-PSI, Jülich, Stockholm, London (Hammersmith), Turku, Kuopio, Uppsala, Brussels, Aarhus.

Others

Behavioural Brain Sciences, School of Psychology, University of Birmingham, UK

Department of Medical Biochemistry & Genetics (IMBG), University of Copenhagen

Department of Pharmacology, Tours University Hospital, France

MAP Medical, Helsinki, Finland

National Cardiovascular Research Center, Osaka, Japan

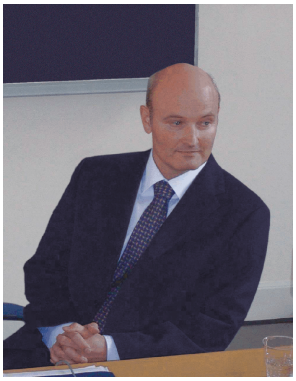
NeuroSearch A/S

Philips Medical Systems

4. Doctoral and PhD Theses

Quantitation of brain metabolism in humans using PET-FDG: levels and limitations

Steen G. Hasselbalch, MD, DMSc



This review deals with quantitation of cerebral glucose metabolism (CMR_{glc}) in humans. It evaluates studies using the Fick principle, where global CMR_{glc} is estimated from arteriovenous differences across the brain multiplied with cerebral blood flow (CBF). These studies are reviewed in relation to tomographic studies of CBF and CMRglc, especially those employing positron emission tomography (PET). PET studies using fluoro-deoxyglucose (FDG) as tracer allow for quantitation of regional CMR_{glc} and methodological aspects of this method have received a great deal of interest, especially with regard to kinetic modelling.

However, few studies have addressed the absolute level of CMR_{glc} obtained by PET-FDG. This review demonstrates that the conversion factor between cerebral metabolic uptake of FDG (CMR_{FDG}) and CMR_{glc}, known as the lumped constant (LC) has attracted far less attention and its determination in previous studies rests on insubstantial evidence. Recent studies in which LC has been determined by dual tracer techniques or by direct comparison between the Fick principle and PET-FDG suggest that the value of LC has been considerably underestimated, leading to an overestimation of CMR_{glc} by PET-FDG. Evidence for a resetting of LC to 0.8 in awake healthy subjects is given. The theoretical background for variations in LC with changes in glucose supply is discussed and exemplified by studies in which LC is shown to change with varying physiological conditions. In conditions, where significant alterations of the cerebral carbohydrate metabolism occur, the determination of CMR_{glc} is further complicated. In starvation induced hypoglycemia, the human brain derives an increasing amount of its energy demand from ketone bodies as their blood level increase during fasting. This adaptation seems not be brought about by hypoglycemia itself, since the same shift in carbohydrate metabolism occurs in acute hyperketonemia. In these conditions, PET-FDG may accurately predict CMR_{glc} only when direct determination of LC is performed in the same study, because changes in blood-brain barrier (BBB) hexose transport and in activities of glycolytic enzymes cause changes in the distribution volumes of FDG and glucose, and subsequently in LC. BBB transport capacity of glucose seems unaffected by high insulin levels, but hyperinsulinemia may cause changes in the distribution of glucose within brain tissue, and its consequences for estimation of CMR_{glc} by PET-FDG is discussed. Finally, in acute or chronic hyperglycemia there is no circumstantial evidence for changes in BBB glucose transport capacity or CMR_{glc}, but changes in LC are demonstrated. In conclusion, this review present evidence for a resetting of the absolute value of global CMR_{glc}. Changes

in BBB glucose transport and CMR_{glc} following changes in substrate supply are discussed. Measuring CMR_{glc} with PET-FDG in these conditions requires determination of LC in order to obtain reliable estimates for CMR_{glc}.

The thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on April 25, 2003, at Rigshospitalet, Auditorium 93. The evaluators were Professor Albert Gjedde and Professor Bjørn Quistorff.

Characterization of serotonin transporter ligands in relation to emission tomography

Betina Elfving, cand.pharm., PhD

This PhD thesis explores possible properties of compounds governing their usefulness as emission tomography ligands. The development and selection of new radioligands is both expensive and time consuming and until now it has - more or less - been based on trial and error procedures. The reason(s) why positron emission tomography (PET) or single photon emission computed tomography (SPECT) ligands fail, as appropriate tracers are only rarely well understood, although a more thorough knowledge of this might be useful in future selections among ligand candidates. Based on current knowledge radiolabeled (S)-citalopram was anticipated to be a suitable PET ligand for the serotonin (5-HT) reuptake site and yet it resulted in an insufficient target-to-background ratio in humans. In this PhD-project, several factors that influences upon the capability of a ligand to apply as a PET/SPECT tracer was investigated, with particular emphasis on (S)-citalopram. These factors include ligand affinity (K_d or K_i), species differences in receptor density (B_{max}) and/or radiotracer affinity, lipophilicity, radiotracer metabolism, radiotracer specific activity, and differential binding to neuronal and glial cell membranes. Further, as anesthesia is almost inevitable in animal PET/SPECT studies, the interference of anesthetics with radioligand binding in neuroreceptor studies was examined. Temperature was found to affect the affinity of selective 5-HT reuptake inhibitors for the 5-HT reuptake site differently and unpredictably. Therefore in vitro binding characterization at 37°C may provide a more realistic value for K_d. Brain tissue homogenate studies conducted at 37°C with [^{3}H]-(S)-citalopram revealed a four times higher affinity and two times higher receptor density in rat as compared to monkey. This means that species differences with regard to ligand affinity and receptor density explain at least partially why radiolabeled (S)-citalopram does not work as a PET ligand. Further, inhibition of cerebral radiotracer metabolism, with subsequent intracerebral trapping of radiolabeled metabolites, was attempted by predosing with the monoamine oxidase inhibitors selegiline and chlorgyline prior to injection of radiolabeled (S)-citalopram. However, the effect of inhibited metabolism could not be separately evaluated since selegiline and chlorgyline turned out to be competitive inhibitors of (S)-citalopram binding to the 5-HT reuptake site. Specific activity and binding

to the glia cells are both factors that may contribute to the insufficient signal seen using radiolabeled (S)-citalopram as a PET ligand. The specific activity was concluded to be less important as the target-to-background ratio of radiolabeled (S)-citalopram remained unaltered when the specific activity was increased more than 10 times compared to a previous study. The same applies for binding to the glia cells. Radiolabeled (S)-citalopram and (+)-McN5652 both displayed lower affinity for the 5-HT reuptake site located glial as compared to neuronal. Since radiolabeled (+)-McN5652 is useful as a PET ligand, binding to the glia cells was concluded to be less important. Furthermore, interference between several anesthetics and radioligands was found. It was concluded that whenever anesthesia is required in neuroreceptor binding studies, interference of the anesthetic with the radioligand binding must be excluded. The interference was anticipated to be radioligand specific.

In conclusion, ligand affinity was found to be of major importance. Because of a relatively low density of 5-HT reuptake sites in the human brain it can be anticipated that a suitable radioligand for use in clinical studies would require a Kd value between 0.03 nM and 0.3 nM in the human brain. In addition, comparison between several successful radioligands show that even given an adequate affinity of the radioligand, other factors may play an additional role, e.g. lipophilicity. This thesis emphasizes the importance of careful consideration of the binding potential (B_{max}/K_d) prior to the selection of a ligand for use in emission tomography studies.

The PhD thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on January 10, 2003, at Rigshospitalet, Auditorium 93. Evaluators were lecturer Per Plenge, Professor Christer Halldin and Associate Professor Per Hartvig.

The PhD-project was completed with Professor, DMSc Gitte Moos Knudsen and lic.pharm., PhD Berith Bjørnholm as supervisors.

Development of new PET and SPECT ligands for visualization of the serotonin transporter in the brain

Jacob Madsen, chemist, PhD

The aim of the project was to develop novel analogues of the selective serotonin reuptake inhibitors citalopram and escitalopram and to radiolabel them for use in emission tomography studies. The main effort was directed towards the synthesis and radiosynthesis of such compounds.

S-[*N*-Methyl-d_3-^{11}C]citalopram was synthesized by reaction between gas phase produced [^{11}C]methyl iodide-d_3 and *S*-desmethylcitalopram. *S*-[*N*-Methyl-^{11}C]citalopram-d_2 (the two deuterium atoms were placed in the side chain α to the nitrogen atom) was synthesized in a reaction between [^{11}C]methyl iodide and deuterium labelled *S*-desmethylcitalopram as precursor. The deuterium labelled precursor was synthesized in 10 steps from escitalopram. *S*-[*N*-Methyl-d_3-^{11}C]citalopram

and *S*-[*N*-methyl-^{11}C]citalopram-d_2 were synthesized to investigate a potential deuterium isotope effect in the metabolism of the radioligands.

Compared to ^{11}C-labelled escitalopram the deuterium labelling of these compounds did not have any effect on the regional brain distribution observed in ex vivo rat studies or in a monkey PET study.

Three new citalopram analogues, where the cyano group in the 5-position was replaced with a 5-methyl, a 5-acetyl or a 5-piperidinyl carbonyl group, were synthesized. Two of these new compounds were successfully radiolabelled.

Radiosynthesis of the ^{11}C-labelled 5-methyl derivative, [5-methyl-^{11}C]{3-[1-(4-fluorophenyl)-5-methyl-1,3-dihydro-isobenzofuran-1-yl]-propyl}-dimethylamine, was achieved in 60-90% decay-corrected radiochemical yield in a Stille reaction with [^{11}C]methyl iodide and the corresponding stannylated derivative. In a monkey PET study the thalamus to cerebellum ratio observed was 1.3.

Radiosynthesis of the ^{11}C-labelled piperidinyl carbonyl analogue was achieved in 62% decay-corrected radiochemical yield applying [^{11}C]carbon monoxide. This radioligand did, however, not cross the blood-brain barrier (Madsen et al., 2003).

[^{125}I]{3-[5-iodo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]propyl}-dimethylamine, a ^{125}I-labelled analogue of citalopram, was synthesized from the corresponding bromo derivative in a Br/^{125}I exchange reaction in 35% radiochemical yield.

Ex vivo rat studies revealed a maximal thalamus to cerebellum ratio of 1.9, which was reached 2 hours after injection. Radio-iodination of the more active enantiomer resulted in a thalamus to cerebellum ratio of 2.4 in *ex vivo* rat studies.

Finally, [^{18}F]bromofluoromethane was synthesized and its use in a palladium mediated cross-coupling reaction with an organostannane was subsequently investigated. This new reaction is very promising and can possibly find interesting applications in fluorine-18 radiochemistry.

Madsen J, Marachtsaki P, Davoodpour P, Bergström M, Långström B, Andersen K, Thomsen C, Martiny L, Knudsen GM. Synthesis and biological evaluation of novel carbon-11-labelled analogues of citalopram as potential radioligands for the serotonin transporter. Bioorganic & Medicinal Chemistry 2003;11:3447-56

The PhD thesis was accepted for evaluation at The Danish University of Pharmaceutical Sciences. The defence took place on May 8, 2003 at the Benzon auditorium, The Danish University of Pharmaceutical Sciences. Evaluators were Professor, PhD Heinz H. Coenen, Chemist, PhD Lise Falborg, and Ass. Professor Bente Frølund.

The PhD-project was completed with PhD Kim Andersen, Professor Mikael Begtrup, Professor, DMSc Gitte Moos Knudsen and PhD Lars Martiny as supervisors.

5. Research Topics

5.1. Cerebral Blood Flow and Metabolism: Experimental Studies

Gitte Moos Knudsen, MD, Professor

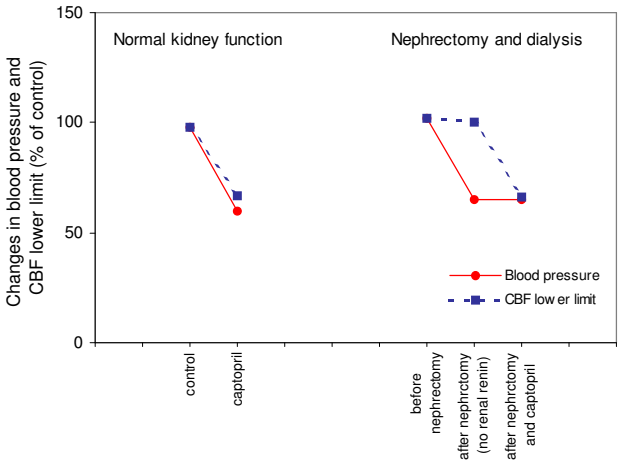
In collaboration with Dept. of Pediatrics, we have established a newborn rat model and the effects of oxygen exposure on cerebrovascular function was investigated. Unrestricted use of oxygen in the delivery room after preterm birth has been associated with reduced cerebral blood flow (CBF) 2 h later. We hypothetized that hyperoxic exposure limits cerebral vasodilation in response to an increase in carbon dioxide tension (PCO_2). To further investigate residual cerebrovascular effects of transient hyperoxia, we monitored cerebral perfusion newborn rats with laser-Doppler flowmetry (LDF) and near-infrared spectroscopy (NIRS). Twenty-four 3- to 5-days-old rats were randomized to either exposure to room air or 100% oxygen for 30 min. Thereafter, following 15 min of stabilization in normoxia, 8% CO_2 was given for 5 min. No significant differences in CO_2 responses were observed between the two groups: mean CBF-CO_2 reactivity as measured by NIRS was 13.3 +/- 3.9%/kPa in the normoxia-group versus 8.8 +/- 4.1%/kPa in the hyperoxia group (NS). The oxygenation index [(HbO_2 - Hb)/2] increased by 0.67 +/- 0.17 micro mol/L/kPa in the normoxia group compared with 1.18 +/- 0.19 micro mol/L/kPa in the hyperoxia group (NS). Cortical perfusion, monitored by LDF, increased by 7.3 +/- 1.5%/kPa versus 6.8 +/- 1.8%/kPa in the normoxia and hyperoxia groups, respectively (NS). We conclude that in newborn rats the CBF-CO_2 reactivity remains intact even after 30 min of oxygen exposure.

Fumagalli M, Mosca F, Knudsen GM, Greisen G. Transient hyperoxia and residual cerebrovascular effects in the newborn rat. Ped Res (In press)

Olaf B. Paulson, MD, Professor

A nephrectomized rat model was developed where the rats could be kept awake and peritoneal dialyzed in a good general condition for a period long enough (48 hours) to allow the elimination of all circulating renin. The model has been used in studies on the physiological effect on the cerebral circulation of the circulating versus the local renin angiotensin system.

Nephrectomy per se caused a significant decrease in arterial blood pressure whereas no changes was seen in the lower limit of cerebral autoregulation (the blood pressure limit below which an additional blood pressure drop results in a decrease of the cerebral perfusion). Following blockade of renin-angiotensin system by the angiotensin converting enzyme (ACE) inhibitor captopril in the nephrectomized animals blood pressure remained stable with no further reduction whereas the lower limit of cerebral blood flow autoregulation decreased. In contrast previous studies in animals with normal kidney function have shown that both blood pressure and the lower limit of cerebral blood flow autoregulation decreased following ACE inhibition.



Schematic presentation of nephrectomy (elimination of renal renin) and ACE inhibition (captopril 10 mg/kg) on blood pressure and lower limit of CBF autoregulation

(The normal kidney function is from previous studies in our laboratory)

These studies indicate that the influence of the renin angiotensin system on the blood pressure is primarily mediated through the renal renin angiotensin system whereas its influence on the cerebral blood flow autoregulation must be mediated primarily through the renin angiotensin system in the cerebral vessels. Bradykinin located in the cerebral blood vessels might contribute to the effect.

Pedersen TF, Paulson OB, Nielsen AH, Strandgaard S. Effect of nephrectomy and captopril on autoregulation of cerebral blood flow in rats. Am J Physiol Heart Circ Physiol. 2003;285:H1097-104

The importance of the extra vascular pH in the brain for the regulation of cerebral blood flow is well-known, e.g., cerebral blood flow increases during hypercapnia. In order to investigate to what extent changes in the cerebrospinal fluid pH influence the perfusion in the brain parenchyma a study was carried out using ventriculocisternal perfusion in the rat. Perfusion with a acid solution (pH 6.8) resulted in a 60% flow increase in contrast to no increase at normal pH (7.4). Further, with the acid CSF perfusion there was a linear relationship between cerebral blood flow and mean arterial blood pressure indicating that autoregulation was abolished. Thus, the acidity in the cerebrospinal fluid can influence the brain parenchyma to such an extent that it increases cerebral blood flow and impairs its autoregulation.

Bay-Hansen R, Ma XD, Hauerberg J, Larsen EH, Juhler M. Effects of cerebrospinal fluid acidity on cerebral blood flow and autoregulation in rats. J Neurosurg Anesth 2003;15:110-8

Laser Doppler flowmetry (LDF) was successfully validated against the intra-arterial ^{133}Xenon injection method for measurements of cerebrocortical CO_2-reactivity and assessment of lower limit of cerebral autoregulation in rats. Under conditions of systemic hemorrhagic hypotension LDF slightly overestimated cerebral blood flow (CBF) compared to simultaneous ^{133}xenon measurements. However, statistically this did not affect assessment of autoregulation lower limit. LDF does not measure CBF quantitatively (mL/g/min), and arbitrary laser Doppler units were normalized to xenon baseline measurements enabling a direct comparison. Since LDF yields continuous data it is very applicable for assessment of relative changes in blood flow such as in autoregulation studies.

Tonnesen J, Pryds A, Larsen EH, Paulson OB, Knudsen GM. Laser Doppler flowmetry validated for measurements of cerebral blood flow in rats: A comparison to the intra-arterial ^{133}xenon injection method. J Cereb Blood Flow Metab 2003;23,suppl.1:106

Delayed structural cerebral sequelae has been reported following high-doses cranial radiation therapy to children with primary brain tumors, but little is known about potential functional changes. For this reason, a study was undertaken in 24 patients previously diagnosed and treated for primary childhood brain tumors. After a median recurrence free survival of 16 years they were examined by positron emission tomography using the glucose analog ^{18}F-fluoro-2-deoxy-D-glucose. Patients treated with both surgery and cranial radiation therapy (44-56 Gy) had a general decreased regional glucose metabolism ($rCMR_{glc}$) compared to normal controls as well as to patients treated with surgery alone. No significant differences was observed between the latter two groups. It is concluded that a general reduction in $rCMR_{glc}$ takes place in long-term recurrence free survivors of childhood primary tumors treated with cranial radiation therapy in high doses.

Andersen PB, Krabbe K, Leffers AM, Schmiegelow M, Holm S, Laursen H, Müller JR, Paulson OB. Cerebral glucose metabolism in long-term survivors of childhood primary brain tumors treated with surgery and radiotherapy. J Neurooncol 2003;63:305-13

5.2. Cerebral Blood Flow and Metabolism: Clinical Studies

Gitte Moos Knudsen, MD, professor

In patients with acute fulminant hepatic failure (FHF) hyperammonemia is consistently found. In addition, patients with FHF frequently hyperventilate spontaneously and this may potentially interfere with cerebral glucose and oxygen metabolism. In this study, we evaluated whether cerebral oxidative metabolism is preserved early in the course of FHF and to what extent mechanical hyperventilation interfered with brain metabolism. Thirteen patients with FHF were included, 5 patients with FHF due to cirrhosis of the liver, and 8 healthy subjects. Concomitant blood sampling from an arterial catheter and a catheter in the jugular bulb and measurement of cerebral blood flow by the xenon 133 wash-out technique allowed calculation of cerebral uptake of glucose (CMR_{glc}) and oxygen ($CMRO_2$). Both CMR_{glc} and $CMRO_2$ were reduced in patients with FHF compared with

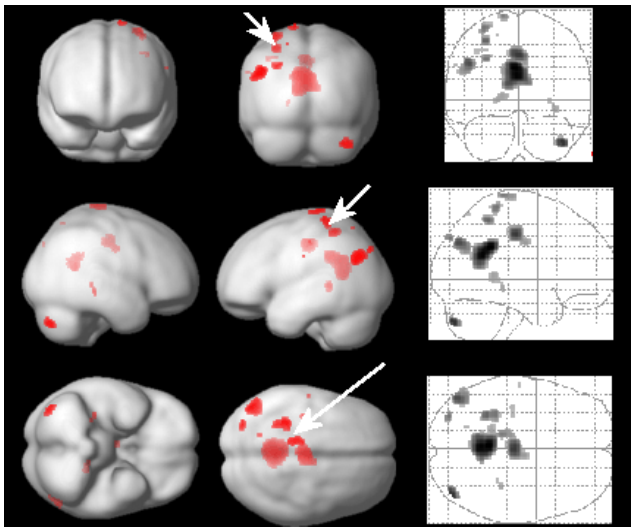
those with cirrhosis and healthy subjects, i.e., 11.8 +/- 2.7 v 18.3 +/- 5.5 and 28.5 +/- 6.6 micromol/100 g/min (P <.05) and 86 +/- 18 v 164 +/-42 and 174 +/- 27 micromol/100 g/min (P <.05). Arteriovenous difference in oxygen and oxygen-glucose index were normal in patients with FHF. Institution of mechanical hyperventilation did not affect glucose and oxygen uptake and hyperventilation did not affect lactate-pyruvate ratio or lactate-oxygen index. In conclusion, we found that cerebral glucose and oxygen consumption are proportionally decreased in patients with FHF investigated before clinical signs of cerebral edema. Our data suggest that cerebral oxidative metabolism is retained at this stage of the disease without being compromised by hyperventilation.

Strauss GI, Møller K, Larsen FS, Kondrup J, Knudsen GM. Cerebral glucose and oxygen metabolism in patients with fulminant hepatic failure. Liver Transpl 2003;9:1244-52

5.3. Brain Mapping

Daniela Balslev, MD, PhD-student

Although the tools we use can extend far away from the body – for instance the head of a tennis racket - we rarely need to see them in order to tell where they are. This functional magnetic resonance imaging (fMRI) study reports on brain areas that associate tool location with hand proprioception. Eleven healthy subjects watched a cursor move on a computer screen and felt the passive movement of the right index finger on a rectangular mouse field. A condition in which cursor and finger location were congruent, as it is the case during the manipulation of a computer mouse, was compared with a control condition with similar sensory stimulation, but in which cursor and finger locations were randomly associated.



Activation foci for tool versus control condition. Statistical parametric map of the t statistic for the difference between conditions (threshold p<0.05, corrected), superposed on inter-subject averaged structural brain image in co-registration with the stereotactic space of the Talairach atlas (left and middle columns) and in glass brain view. The arrow points to activation foci in the postcentral gyrus/superior parietal cortex, at (x y z) coordinates (-32 -38 66), (-14 -32 78), (-12 -24 76), (-58 -16 32) and (-40 -22 46)

There was no significant difference between conditions in duration or speed of finger movement. At several left parietal sites including the hand area in the postcentral gyrus the neural activity was increased in the tool condition compared with the control

condition. These areas thus appear to integrate spatially congruent visual and proprioceptive stimuli, suggesting that external objects moving in spatial alignment with the limbs are accommodated into somatic representations.

Balslev D, Nielsen FÅ, Law I, Paulson OP. Tool proprioception at your fingertips – somatosensory representations for tool location. Conference paper, winner of a Graduate Student Award at the 4th Annual Meeting of the International Multisensory Research Forum, 2003

5.4. Cerebral Neuroreceptors: Radiosynthesis and Experimental Studies

Susana Aznar, Biologist, PhD

Experimental neuroreceptor studies that, from an anatomical and cellular point of view, characterize and describe the localization and role of the different serotonin receptors in the brain as well as its interaction with other receptor systems are being conducted. Primarily, we make use of in vivo experimental studies where we apply neuronal tracing and double and triple immunostaining techniques.

The projection of raphe fibres to inhibitory interneurons in areas involved in controlling and maintaining hippocampal activity have also been characterized in detail. The hippocampus is important for spatial and memory formation. By using neuronal tracing techniques we found that the hippocampal neurons receive a significant non-serotonergic raphe projection besides the well-described serotonergic projection. These results indicate that the control that raphe nuclei exert on hippocampal and septal activity may not be mediated exclusively through a serotonergic pathway, but other neurotransmitter systems may also be involved.

Aznar S, Qian Z-X, Knudsen GM. Non-serotonergic dorsal and median raphe projection onto parvalbumin- and calbindin-containing neurons in hippocampus and septum. Neuroscience, in press

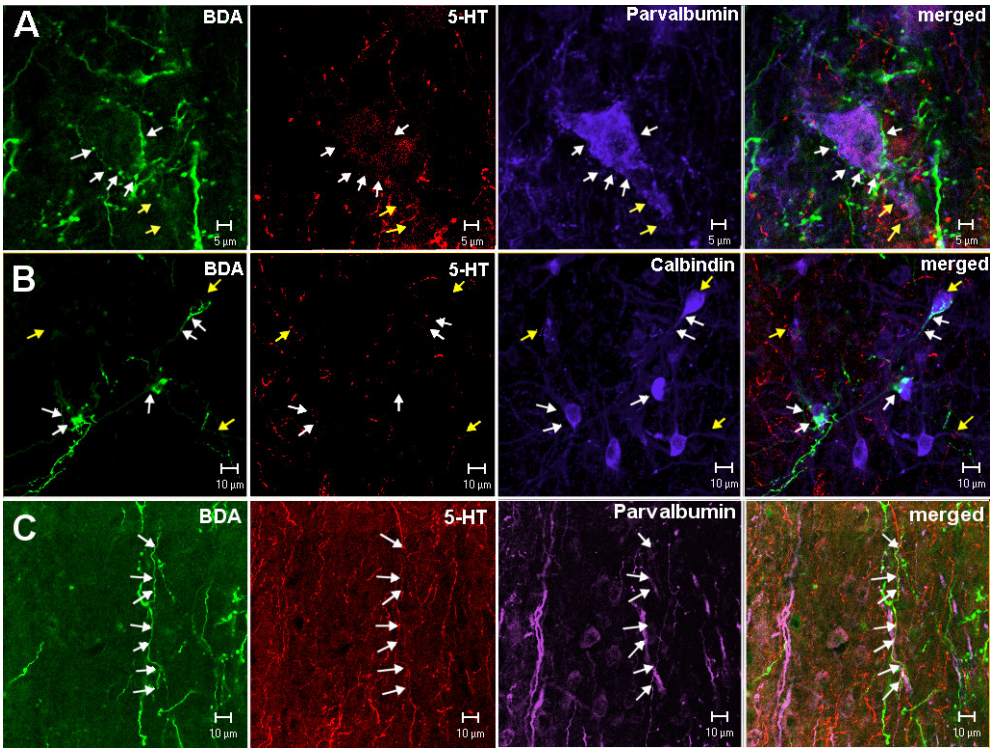
In another study we have investigated how the serotonergic and the cholinergic systems interact with each other. Our results indicate that α7 nicotinic receptors, which are very important in relation to Alzheimer's disease, are present in serotonin neurons projecting to hippocampal and septal areas.

Aznar S, Knudsen GM. Alpha-7 acetylcholine nicotinic receptor subunit is localized in serotonergic neurons projecting to hippocampus and medial septum/Diagonal Band of Broca complex. Program No. 46.9. 2003 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2003. Online

In a parallel study, acetylcholine levels were increased after administration of acetylcholinesterase inhibitors in rats. The induced neuronal activation was attenuated in the hippocampus when at the same time the serotonergic system was inhibited. These results indicate that the cholinergic system exerts its effect on neuronal activation partly through activation of the serotonergic system.

Rahbek B, Knudsen GM, Moller A, Aznar S. Neuronal activation induced by Rivastigmine in the rat hippocampus is partly mediated via the serotonergic system. Program No. 731.12. 2003 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2003. Online

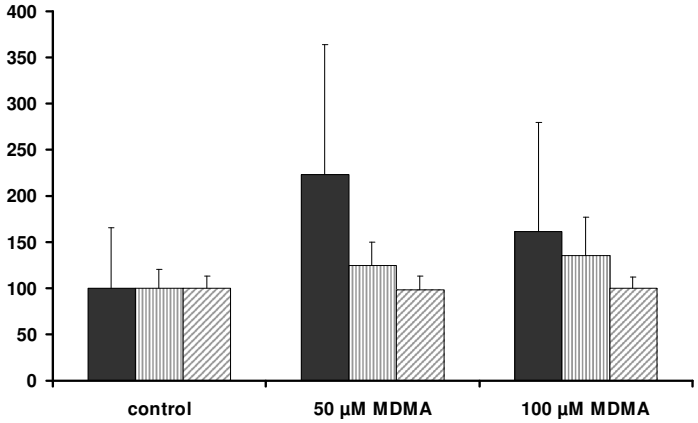
We have investigated the localization and distribution of the 5-HT_{1A} receptor in different neuronal subtypes throughout the rat forebrain. This is important for the understanding of both the role of this receptor in neuronal circuitries and the effect 5-HT_{1A} receptor activation has on brain activity. With the help of immunocytochemical double-labeling techniques, we have shown that the 5-HT_{1A} receptor is present on both pyramidal and principal cells and different subtypes of inhibitory interneurons. Our finding that the receptor is present in certain groups of parvalbumin-containing interneurons that are involved in controlling neuronal firing activity suggests an important role of the 5-HT_{1A} receptor in modulating specific brain functions.



Non-serotonergic dorsal and median raphe fibers projecting onto parvalbumin and calbindin positive neurons in septum: Confocal images of dorsal raphe BDA-labeled fibers making contacts (white arrows) with a parvalbumin- (A) positive cell in medial septum/diagonal band of Broca, and with calbindin-positive cells in lateral septum (B). Triple labeling for serotonin shows how BDA-labeled fibers contacting these cells are non-serotonergic. In C, an example of a serotonin-positive BDA-labeled fiber is shown. Yellow arrows show serotonin positive fibers contacting calbindin and parvalbumin positive neurons. In B the framed area shows a detail at higher magnifications of the calbindin positive neuron. Scale bar A = 5 µm, B, C = 10 µm, framed area=5µm

Aznar S, Qian Z-X, Shah R, Rahbek B, Knudsen GM. The 5-HT_{1A} serotonin receptor is located on calbindin- and parvalbumin-containing neurons in the rat brain. Brain Research 2003;959:58-67

In an organotypic culture model we have investigated the effect of MDMA (ecstasy) on neuronal cell death and its effect on 5-HT_{2A} serotonin receptor levels. We found no toxic effect of MDMA in this in vitro model, and no change of 5-HT_{2A} receptor levels after exposure to MDMA.



Number of Fluoro-Jade stained cells, and densities of MAP2 and 5-HT_{2A} immunostaining (mean±s.e.m) measured in sections of organotypic hippocampal cultures exposed to control medium and to various concentrations of MDMA for 1 week

Sveen ML, Knudsen GM, Aznar S. No effect of MDMA (ecstasy) on cell death and 5-HT_{2A} receptor density in organotypic rat hippocampal cultures. Neuroscience Letters (in press)

Betina Elfving, Pharmacologist, PhD

Interference of anesthetics with radioligand binding was investigated in experimental studies. Animal studies are usually carried out in the initial steps of the evaluation of new emission tomography ligands and in order to keep the animals in a restricted position during the scan session, anesthesia is almost inevitable.

In ex vivo rat studies we studied the interference of ketamine/xylazine, zoletile-mixture, isoflurane, and halothane with the serotonin (5-HT) reuptake site, the 5-HT_{2A} receptor and the dopamine (DA) reuptake site by use of [^{3}H]-(S)-citalopram, [^{18}F]altanserin, and [^{125}I]PE2I, respectively.

We found interference between several anesthetics and the 5-HT and DA reuptake site. This interference may be radioligand specific. It is concluded that prior to conduction of neuroreceptor radioligand studies the possible interaction between radioligands and anesthetics should be carefully evaluated.

Elfving B, Bjørnholm B, Knudsen GM. Interference of anaesthetics with radioligand binding in neuroreceptor studies. European Journal of Nuclear Medicine and Molecular Imaging 2003; 30:912-915

5.5. Cerebral Neuroreceptors: Clinical Studies

Gitte Moos Knudsen, MD, Professor and Steen Hasselbalch, MD, Consultant

NRU coordinates a concerted action within the European Commission 5th framework dealing with neuroreceptor imaging in patients with *mild cognitive impairment* with the objective to be able to establish an early diagnosis and a prognosis for the development of Alzheimer's disease. More information is provided on the website www.mci.nru.dk.

In healthy subjects, a number of different receptor systems show a moderat decline with age whereas in Alzheimer's disease (AD) many of these receptor systems show marked reductions. Mainly based on postmortem studies decreases in 5-HT_2 receptors, nicotinic α4-β2, and a preferential loss of M2 as compared to M1 muscarinic receptors have been shown. Some of these findings have been partially replicated in in-vivo imaging studies but the heterogeneity of the patients, the small samples sizes, and problems with shortcomings in the radiotracer characteristics have so far been limiting factors for the overall progress within the field. Molecular imaging methods hold a very high potential as powerful tools for demonstrating more basic pathophysiological processes. It is anticipated that with the rapid development of better, quantifiable, and specific tracers, also including probes for detection of abnormally increased amyloid accumulation, molecular imaging will be able to contribute substantially to bridge between at one hand the enormous progress seen at the molecular level with that of the clinical entity of AD. It will also continue to provide an efficient tool for diagnosing and monitoring disease progress and treatment efficacy.

Although specific clinical criteria for primary neurodegenerative disorders, i.e. AD, Lewy body dementia (DLB), and frontotemporal dementia (FTD) exist, these have limited sensitivity and specificity. Attempts have been made to increase the diagnostic accuracy using specific markers for these disorders, including PET studies using tracers for various neuroreceptor systems. In DLB cholinergic and dopaminergic dysfunctions have been established, and in FTD reductions in serotonergic receptors and dopamine reuptake are among the neurochemical changes.

The unique possibility to couple symptoms in clinically well-characterized patients with specific transmitter dysfunctions increase our understanding of behavioral and neuropsychiatric symptoms found in these disorders. Further, neurotransmitter imaging may help in the early diagnosis or in the differential diagnosis between the dementing disorders.

Knudsen GM. Assessment of neuroreceptor changes in healthy ageing and in Alzheimer's disease with emission tomography. In Abe K, et al, eds. Molecular Mechanism and Epochal Therapeutics for Ischemic Stroke and Dementia. Int Congress Series 2003;1252:299-308

Hasselbalch SG. Neuroreceptor imaging with positron emission tomography in dementia. Review Series Dementia 4/2003.

Lars Hageman Pinborg, MD

Since 2000, NRU has in collaboration with the PET and Cyclotron Unit at Rigshospitalet, conducted more than 150 [^{18}F]altanserin-PET studies in neuropsychiatric patients and healthy controls. [^{18}F]altanserin is a PET-tracer with high selectivity for the 5-HT$_{2A}$ receptor compared to other monoamine receptors. The vast majority of these studies have been conducted using a bolus/infusion approach developed at NRU. Compared to administration of [^{18}F]altanserin as a single bolus, administration of [^{18}F]altanserin as a combination of an initial bolus injection followed by a constant infusion offers advantages in terms of both experimental and analytical simplicity. In addition, the bolus/infusion approach allows for monitoring of the effect of pharmacological challenges during a single scan session. For quantification of [^{18}F]altanserin binding to the 5-HT$_{2A}$ receptor, the bolus/infusion approach is particular well suited, since it allows for simple correction for labeled metabolites of [^{18}F]altanserin passing the blood-brain-barrier. To correct for labeled metabolites of [^{18}F]altanserin passing the blood-brain-barrier we used cerebellum as a representation of free and non-specifically bound [^{18}F]altanserin and its metabolites.

Pinborg LH, Adams KH, Svarer C, Holm S, Hasselbalch SG, Haugbol S, Madsen J, Knudsen GM. Quantification of 5HT$_{2A}$ receptors in the human brain using [^{18}F]altanserin and the bolus/infusion approach. J Cereb Blood Flow Metab 2003;23:985-996

In a separate human study, we tested the effect of acute changes in the extracellular concentration of 5-HT upon [^{18}F]altanserin binding to the 5-HT$_{2A}$ receptor. One hour after [^{18}F]altanserin steady-state was attained in brain and plasma, the selective serotonin reuptake inhibitor, citalopram was administered to all subjects as a constant infusion for 20 minutes. To reduce 5-HT$_{1A}$ mediated autoinhibition of cortical 5-HT release four of the seven subjects were pretreated with the partial 5-HT$_{1A}$ agonist pindolol for three days at an increasing oral dose (25 mg on the day of the PET scanning). Despite a pronounced increase in plasma prolactin and two subjects reporting hot flushes compatible with an 5-HT induced adverse effect, cortical [^{18}F]altanserin binding was insensitive to the citalopram challenge, even after pindolol pre-treatment.

Pinborg LH, Adams KH, Hasselbalch SG, Holm S, Yndgaard S, Svarer C, Knudsen GM. It it not possible to measure acute fluctuations of 5HT using [^{18}F]altanserin-PET and citalopram. J Cereb Blood Flow Metab (in press)

Finally, we reported the initial results from our [^{18}F]altanserin-PET database of 5-HT$_{2A}$ in normal volunteers. At the time of submission 52 healthy subjects aged between 21 and 79 years were included. The relation between binding parameters and a number of methodological and demographic variables was studied to aid the design and interpretation of clinical studies of the 5-HT$_{2A}$ receptors. [^{18}F]-altanserin binding appears not to be influenced by gender, but the effects of ageing must be taken into account when designing clinical studies, as a significant decrease in 5-HT$_{2A}$ receptors is found as a consequence of normal ageing (6% decrease in [^{18}F]altanserin binding per decade) and in addition, a confounder in terms of an apparent increase in cerebellar non-specific binding and/or

increase in 5-HT_{2A} receptor density is present. Finally, correlations between BMI and [^{18}F]altanserin binding in several frontal and temporal cortex regions were demonstrated.

Adams KH, Pinborg LH, Hasselbalch S, Svarer C, Holm S, Knudsen GM. A database of [^{18}F]-altanserin binding to 5-HT_{2A} receptors in normal volunteers: Normative data and relationship to physiological, and demographic variables NeuroImage (in press)

5.6. Implementation of Methods for Analysis of Brain Data

Esben Høgh-Rasmussen, MSc, PhD-student, Thomas Rask, MSc-student, Robin de Nijs, MSc, Matthew G. Liptrot, MSc, Tim Dyrby MSc, and Claus Svarer, PhD, MSc.

The data analysis section is involved in optimising data acquisition, reconstruction and handling of images from the Marconi/Philips SPECT scanner for getting the best obtainable signal-to-noise ratio in the images. Especially, reconstruction of dynamic images including correction for scatter, and attenuation as well as calibration of the scanner is a problem using the software provided with the scanner.

The data analysis section is also involved in a number of common European projects. In the NCI-MCI project data sets from the five participating centres will be analysed in a common and standardised way using automatic tools for extraction of regions of interest extracted data.

The other EU project, the PVEOut project has been extended and expires in 2004. The data-analysis section at NRU has together with the group from Naples been selected to implement the final version of the pipeline software to control the partial volume error (PVE) correction process. This software will include modules for interfacing to public domain and own developed software that can be used for partial volume correction of functional PET data. This includes modules for co-registration, segmentation, reslicing, definition of regions and partial volume correction.

In a PhD study that was initiated last year it is investigated whether a better precision in partial volume correction can be achieved including the high-resolution structural information in the reconstruction process leaving out the traditional low-pass filtering. This project is scheduled for another two years.

Furthermore, the data analysis section has been working with automatic methods for identification input curves for kinetic modelling instead of using arterial sampling. Using clustering methods it has been possible to identify intravascular brain voxels and to track the venous activity over time.

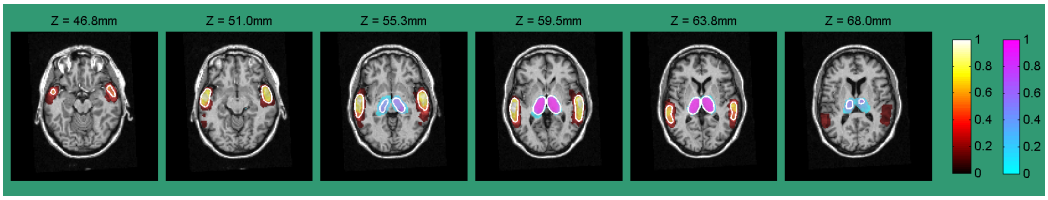
Liptrot M, Adams KH, Martiny L, Pinborg LH, Lonsdale MN, Olsen NV, Holm S, Svarer C, Knudsen GM: Cluster analysis in kinetic modelling of the brain: a non-invasive alternative to arterial sampling. NeuroImage (in press)

A method for probability map based volume of interest (VOI) set definition has been developed. Using structural MR scans template VOI sets are transferred to new subjects, making it superfluous to manual delineate VOI's on new subjects own structural scan. In this study, it is shown that the variation in the generated VOI set can be lowered using

multiple template VOI sets. From multiple transformed template VOI sets a probability map for each VOI is generated. Transforming more than one VOI set to 'new subject space' has been shown to improve reproducibility of the generated VOI sets. Both the variation coming from small 'errors' made when manually delineating VOI sets in 'template space' and errors made when identifying the transformation from 'template space' to 'new subject space' is decreased. Further, it is shown how thresholding of the probability maps avoid biasing the volume of the generated VOI sets.

Svarer C, Adams KH, Hasselbalch SG, Madsen K, Knudsen GM. Tuning automatic ROI-set generation in the brain. Society of Nuclear Medicine; New Orleans, LA, USA. Reston, VA, USA: Society of Nuclear Medicine; 2003

Svarer C, Adams KH, Hasselbalch SG, Madsen K, Pinborg LH, Knudsen GM. Comparing ROI volume changes using automatic and manual ROI delineation methods. J Cereb Blood Flow Metab 2003;23,suppl.1:620



Probability maps generated from 10 transferred template VOI sets for the thalamus (cool color scale) and superior temporal cortex (hot color scale). As expected the figure shows that VOI center voxels have high probability while more exterior voxels have lower probabilities. These probability maps are thresholded for generating the final transferred VOI sets in new subject space as indicated by the white lines

6. Publications

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Andersen PB, Krabbe K, Leffers AM, Schmiegelow M, Holm S, Laursen H, Müller JR, Paulson OB. Cerebral glucose metabolism in long-term survivors of childhood primary brain tumors treated with surgery and radiotherapy. J Neurooncol 2003;63:305-13.

Bay-Hansen R, Ma XD, Hauerberg J, Larsen EH, Juhler M. Effects of cerebrospinal fluid acidity on cerebral blood flow and autoregulation in rats. J Neurosurg Anesth 2003;15:110-8.

Pedersen TF, Paulson OB, Nielsen AH, Strandgaard S. Effect of nephrectomy and captopril on autoregulation of cerebral blood flow in rats. Am J Physiol Heart Circ Physiol 2003;285:1097-104.

Strauss GI, Møller K, Larsen FS, Kondrup J, Knudsen GM. Cerebral glucose and oxygen metabolism in patients with fulminant hepatic failure. Liver Transpl 2003;9:1244-52.

Neuroreceptor Studies

Aznar S, Qian Z, Shah R, Rahbek B, Knudsen GM. The 5-HT1A serotonin receptor is located on calbindin- and parvalbumin-containing neurons in the rat brain. Brain Res 2003;959:58-67.

Elfving B, Bjørnholm B, Knudsen GM. Interference of anaesthetics with radioligand binding in neuroreceptor studies. Eur J Nucl Med 2003;30:912-5.

Madsen J, Marachtsaki P, Davoodpour P, Bergström M, Långström B, Andersen K, Thomsen C, Martiny L, Knudsen GM. Synthesis and biological evaluation of novel carbon-11-labelled analogues of citalopram as potential radioligands for the serotonin transporter. Bioorganic & Medicinal Chemistry 2003;11:3447-56.

Pinborg LH, Adams KH, Svarer C, Holm S, Hasselbalch SG, Haugbøl S, Madsen J, Knudsen GM. Quantification of 5-HT2A receptors in the human brain using [18F]Altanserin-PET and the bolus/infusion approach. J Cereb Blood Flow Metab 2003;23:985-96.

Textbooks and Reviews

Højgaard L, Eigtved A, Paulson OB. Brain metastases, intracranial lymphomas, and nongliomatous tumors. In: Von Schulthess GK, ed. Clinical molecular anatomic imaging. Philadelphia: Lippincott Williams & Wilkins, 2003:169-74.

Hasselbalch SG. Neuroreceptor imaging with positron emission tomography in dementia. Review Series Dementia 4/2003.

Knudsen GM. Assessment of neuroreceptor changes in healthy ageing and in Alzheimer's disease with emission tomography. In Abe K, et al, eds. Molecular Mechanism and Epochal Therapeutics for Ischemic stroke and Dementia. Int Congress Series 2003;1252:299-308.

7. Other Activities

7.1. Congress Participation

The staff of NRU has participated in 22 international meetings and congresses related to their research fields. Staff members have participated as evaluators of abstracts and as chairmen at scientific sessions.

7.2. Congress Organizing

NRU organized session 17: 'Measuring acute fluctuations of neurotransmitter concentrations using PET and SPECT: a new approach' at the 23th European Winter Conference on Brain Research, Les Arcs, March 2003.

7.3. Pre- and Postgraduate Teaching

The XVth annual PET Pharmacokinetic course, Montreal Neurological Institute, Canada (faculty member Gitte Moos Knudsen).

NRU organizes every other week seminars open to the public within the areas of NRU research interests. The meetings are announced on the homepage http://nru.dk/meetings/FIG.

On December 12, 2003, NRU organized an open-to-the-public one day symposium where scientists from NRU presented their most recent data.

Pregraduate Supervision:

OSVAL 1: Medical student Louise Iversen: Den cerebrale autoregulation ved hypertension. Supervisor: Olaf B. Paulson

OSVAL 2: Medical student Kirsten Nielsen: Localization of the serotonin transporter on glial and neuronal cells. Supervisor: Gitte Moos Knudsen

OSVAL 2: Medical student Birgitte Louise Bech. Personality and the neurotransmitter systems. Supervisor: Gitte Moos Knudsen

OSVAL 2: Medical student Lone S. Hove: Demensdiagnostik med MMSE. Supervisor: Steen G. Hasselbalch

OSVAL 2: Medical student Kenneth Nielsen: Farmakologisk behandling af kognitive symptomer ved demens af Alzheimers type. Supervisor: Steen G. Hasselbalch

Master thesis human biology: Birgitte Rahbek: The role of the serotonergic system in acute treatment with the acetylcholinesterase inhibitor Rivastigmine. Supervisors: Susana Aznar and Gitte Moos Knudsen

Pregraduate medical thesis: Medical student Haroon Arfan. In vivo imaging of the 5-HT_{2A}receptors of the human brain in healthy twins: A positron emission tomography study with [^{18}F]altanserin. Supervisor: Gitte Moos Knudsen and Per Kragh-Sørensen, OUH.

Cell Biology Project II: Human biology student Anders Bue Marcussen. Therapeutic use of stem cells in the treatment of Parkinson´s disease. Supervisor: Gitte Moos Knudsen.

Cell Biology Project II: Human biology student Niels Henning Skotte. The etiology and pathogenesis of Parkinson's disease. Supervisor: Gitte Moos Knudsen.

7.4. National and International Committees

National Committees:

Chairman, Department of Clinical Neuroscience and Psychiatry, University of Copenhagen (Olaf B. Paulson)

Chairman of the Research Committee of the Neuroscience Centre at Rigshospitalet (Olaf B. Paulson)

Secretary of the Danish Society of Neuroscience (Olaf B. Paulson)

Board Member of the Danish Neuroscience Society (Gitte Moos Knudsen)

Board Member of the Danish Alzheimer Association (Olaf B. Paulson)

Chairman of the Research Committee of the Danish Alzheimer Association and Member of the Danish Alzheimer Research Foundation (Olaf B. Paulson)

Member of the Neurology Committee of the Copenhagen Hospital Corporation (Olaf B. Paulson)

Member of the Health Science Faculty Research Council, Copenhagen University (Gitte Moos Knudsen)

Board Member of the Copenhagen Neuroscience School (Gitte Moos Knudsen)

Member of Rigshospitalets Medical Council (Gitte Moos Knudsen)

Member of the committee for implementation of clinical neuroscience and psychiatry in the new curriculum for the physician education at the University of Copenhagen (Olaf B. Paulson)

International Committees:

Secretary of the International Society for Cerebral Blood Flow and Metabolism (Gitte Moos Knudsen)

Member of the European Federation of Neurological Societies Working Group on Brain Imaging (Olaf B. Paulson)

Member of the Programme Committee for the Federation of European Neuroscience Society's annual meeting in Lisbon in 2004 (Olaf B. Paulson)

Evaluation:

Member of the Editorial Board of the Journal of Cerebral Blood Flow and Metabolism (Gitte Moos Knudsen)

Evaluator of PhD-thesis: Miriam Kolko, MD (Gitte Moos Knudsen)

Evaluator of doctoral thesis: Per Lav Madsen, MD (Gitte Moos Knudsen)

Evaluator of doctoral thesis: Marie-Louise Moes Grønholdt (Gitte Moos Knudsen)

Evaluator for the Swedish Medical Research Council (Olaf B. Paulson)

Evaluator for the British Medical Research Council (Olaf B. Paulson)

Evaluator of PhD-thesis: Szymkowiak Have, engineer (Claus Svarer)

External examiner at the Technical University of Denmark (Claus Svarer)

Finally, staff members of NRU regularly conduct peer-reviews for several international journals and at international congresses.

7.5. Awards

Professor Olaf B. Paulson received on February 25, 2003 the Lundbeck Prize 2002 for outstanding neuroscience research.

Presentation of the Lundbeck Prize. From left to right: Sven Dyrløv Madsen, President of the Lundbeck Foundation, Olaf B. Paulson, and Mikael Rørth, Member of the Council of the Lundbeck Foundation.

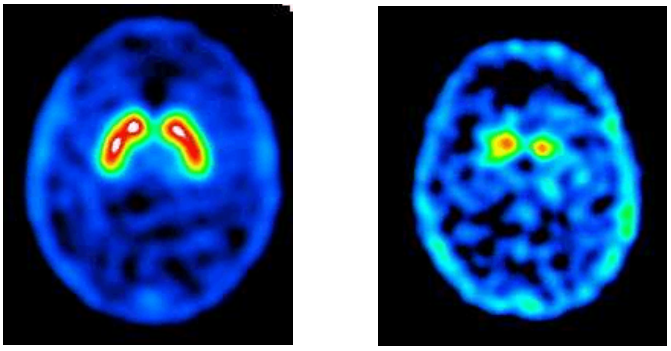
Daniela Balslev received a Graduate Student Award at the 4th Annual Meeting of the International Multisensory Research Forum, 2003 for the abstract: Balslev D, Nielsen FÅ, Law I, Paulson OP. Tool proprioception at your fingertips – somatosensory representations for tool location.

8. SPECT Laboratory

The implementation of the new Philips IRIX SPECT-scanner has continued. A part-time physicist, Robin de Nijs, has been engaged for conduction of further developments and to manage the contract responsibilities with Philips.

A total of 325 scans have been performed in 2003 and the following new clinical procedures have been implemented:

- Dopamine transporter ligand ^{123}I-PE2I as a diagnostic tool in work-up of the parkinsonistic patient
- Interictal and ictal SPECT scan on children as a clinical tool in the presurgical work-up



Dopamine transporters as measured with ^{123}I-PE2I SPECT.
Left: Healthy control, Right: Patient with mild Parkinson's disease

Research projects carried out in 2003

- Database, healthy controls with and without transmission scan correction
- Development of steady-state quantification of dopamine receptors with ^{123}I-PE2I
- Investigations of the serotonin transporter with ^{123}I-ADAM
- Pig studies of the serotonin transporter with ^{123}I-citalopram
- Cerebral blood flow changes in a patient cohort from the Memory Clinic

9. Prospects

In 2004, there will continue to be new tasks and challenges for NRU. At the SPECT laboratory, we are currently improving the data analysis and presentation for the patient file reports. We hope to be able to implement software for SPECT image subtraction and to establish a reference material for ^{99m}Tc-SHMPAO-SPECT consisting of healthy subjects. The PET-unit at Rigshospitalet has finalized a substantial expansion of their radiochemistry facilities, and advanced equipment for radiochemistry synthesis is about to be implemented. This is anticipated to profoundly increase the speed with which new radioligands are introduced and used.

Several of our scientific staff members will, in 2004, complete their term at NRU. Karen Adams will defend her PhD-thesis in April, and another two PhD-theses are expected to be submitted during 2004. A new professor in clinical neurobiology and chief consultant at the department of neurology is expected to be appointed by the University of Copenhagen and Rigshospitalet during 2004. This professor will be attached to NRU and replace the previous time limited position.

Finally, we are looking forward to reinforce our collaboration both with previous and new international collaborators and with research colleagues in the Copenhagen University Priority Area: Body and Mind.

NRU staff September 2003

10. Acknowledgements

The Neurobiology Research Unit has received generous support from a number of public and private research funds.

Augustinusfonden
Beckett Fonden
Danish Medical Research Council
Danish Research Agency
Danish Research Council for the Humanities
Den Lægevidenskabelige Forskningsfond for Storkøbenhavn, Færøerne og Grønland
Direktør Jacob Madsen og hustru Olga Madsens Fond
Familien Hede Nielsens Familiefond
Fonden for Neurologisk Forskning
Fondsbørsvekselerer Henry Hansen og hustru Karla Hansen, f. Westergaards legat
H:S - Copenhagen Hospital Corporation
Hørslevfonden
Ludvig og Sara Elsass Fond
M.L. Jørgensen og Gunnar Hansens Fond
NeuroSearch
Novo Nordisk Fonden
Otto Mønsteds Fond
Rigshospitalets Jubilæumsfond
Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat
Simon Fougner Hartmanns Familiefond
Speciallæge i neurologi Jørgen Wendelboe-Jørgensen og Laura Wendelboe-Jørgensens Fond
The Estate after Inge Arndal
The Health Insurance Foundation
The Lundbeck Foundation
The Research Council of Rigshospitalet
University of Copenhagen, Faculty of Health Sciences

International research funding:
EU 5th Framework program

11. Dansk Resumé

Vi håber, du har haft fornøjelse af at læse denne årsrapport fra Neurobiologisk Forskningsenhed (NRU), og at rapporten har givet et godt indtryk af forskningsenhedens aktiviteter. Et kort resumé gives nedenfor.

I løbet af 2003 har overlæge Steen G. Hasselbalch forsvaret sin doktordisputats 'Quantitation of brain metabolism in humans using PET-FDG: levels and limitations'. Denne afhandling, der bygger på et antal metodologisk elegante og logisk opbyggede arbejder, repræsenterer en fornem afslutning på mange års indsats. Afhandlingens indhold vil utvivlsomt blive internationalt anerkendt som et væsentlig bidrag til litteraturen vedrørende korrektionsfaktoren til anvendelse til beregningen af hjernens regionale glukosestofskifte udfra fluorodeoxy-glukose-metoden med PET.

To PhD-studier er endvidere blevet afsluttet ved afhandlinger: I maj forsvarede radiokemiker Jacob Madsen sin afhandling, der omhandler udvikling af nye radiomærkede sporstoffer til afbildning af hjernens serotonintransporter med PET. Farmaceut Betina Elfving forsvarede i januar sin afhandling, der ligeledes omhandlede sporstoffer for serotonintransporteren, her med særlig vægt på årsagsforklaringer af, hvorfor sporstoffet ^{11}C-citalopram ikke er anvendeligt som PET-sporstof.

Ved NRU har vi en meget dygtig og stabil gruppe af bioanalytikere og sekretærer, der er af væsentlig betydning for forskergruppens succes. I den forbindelse er det en glæde at kunne konstatere, at NRU's ledende bioanalytiker, Gerda Thomsen, sideløbende med sit job som daglig leder i SPECT-laboratoriet, var i stand til at afslutte Rigshospitalets lederuddannelse med udmærkelse.

Det var endvidere en stor glæde for hele forskningsenheden, at professor Olaf Paulson i februar blev tildelt den hæderfulde Lundbeckpris for hans mangeårige indsats inden for hjerneforskning. Overrækkelsen af prisen skete i forbindelse med en velbesøgt reception afholdt på Rigshospitalet. Olaf Paulsons foredrag omhandlede hans omfattende forskning inden for hjernens gennemblødnings autoregulation og sluttede med en oversigt over 'brain mapping'.

Københavns Universitet har besluttet at udnævne forskningstemaet 'Krop og Bevidsthed' som et særligt indsatsområde. Dette konsortium er sammensat tværdisciplinært med tværfakultær involvering. Konsortiet blev indviet i 2003, og vi forventer et frugtbart nyt samarbejde via dette satsningsområde.

Slutteligt vil vi gerne benytte anledningen til at takke de mange fondsydere, der har støttet NRU's forskning. Uden denne støtte ville store og væsentlige dele af NRU's forskning ikke kunne gennemføres.