Scientific Programme

02.04.2017

Highlight session
09:00 – 10:00 Max Kade Auditorium

Presidential Lecture

Peter Herscovitch, United States

Tracking the molecular pathology of Alzheimer's Disease with PET 09:00 – 10:00
William J. Jagust, United States

Poster viewing
10:00 – 11:00 Exhibition & Poster Area

Poster viewing session I

PS01-041 **The importance of cerebral metabolic rate of lactate**
Gerd Krüger, Germany
Starting with lack of O2 studies on the transport of glucose into the brain in rats in the 70s we underestimated brain lactate as less efficient in contrast to the oxidation of glucose. But there remains a not [...]really been resolved question about the role of lactate: Can lactate overcome the lack of energy caused by a reduced oxidative metabolism only by increasing the rate of glycolysis? Now, great evidence from *in vitro* and *in vivo* experiments lactate is a fuel source on enhanced transport from the blood into the brain and may help energetically the neurons by oxidation. In the 80s we predated the importance of cerebral metabolic rate (CMR) of lactate (lac) as significant indicator for impaired cerebral metabolism.
155 patients with organic brain syndromes of degenerative, vascular, (alcohol)toxic and other etiologies were classified by cluster analysis according to rating variables of the AMDP system. Blood-flow was determined by a modification of the method of Kety and Schmidt and enabled to measure CMRs lactate, glucose and oxygen.
Brain oxidative metabolism differed significantly within the classified syndromes (**p (u) =0.001**): CMR lactate was half of normal in the depressive patients and much higher in the patients with organic core symptoms, highest in (alcohol)toxic; delusional patients showed similar changes as the depressives. Multi-infarct- patients were predominating these syndromes.
Deleteriously impaired lactate metabolism, increased or decreased, are not able to account for around 10-12 % in the adult human brain. Therefore, mental fitness has not been saved. There are obvious (pre)morbid clinically correlated biochemical warnings comparing statistically derived clinical data of so-called "organic brain syndromes", particularly, by CMR of lactate.

PS01-044 **Effects of omega-3 fatty acids on resting cerebral perfusion in patients with mild cognitive impairment**
Claudia Schwarz, Germany
Objectives: Alteration of cerebral perfusion is a pathologicalfeature of mild cognitive impairment (MCI) (1) that canpotentially be targeted by long-chain omega-3 fatty acids (FA) supplementation.Previous studies showed that omega-3 FA supplementation has the potential toincrease cerebral perfusion in animals as well as in healthy humans (2). Therefore,this randomized, placebo-controlled, double-blinded proof-of-concept studyassessed effects of omega-3 FA on resting cerebral perfusion in MCI patients.
Methods: In thirteen patients with MCI (omega group: n = 5;placebo group: n = 8), who completed a 26-

weeks intervention, resting cerebralperfusion (cerebral blood flow and cerebral blood volume) was measured beforeand after intervention, using dynamic susceptibility contrast magneticresonance imaging of the brain at 3T.
Results: The omega group showed on average a sizable increaseof cerebral blood flow (26.0 % ± 22.4) and cerebral blood volume (17.8 % ± 13.3)within combined regions-of-interest typically affected in Alzheimer's disease,which was not observed in the placebo group, neither for cerebral blood flow (1.9 %± 23.8) nor for cerebral blood volume (5.4 % ± 21.0).
Conclusions: These preliminaryfindings suggest that omega-3 FA supplementation may potentially improve cerebral perfusion in patients that suffer from MCI,often a precursor of Alzheimer's disease, and thus have the potential to delayor even prevent further cognitive decline and the conversion to Alzheimer's disease. Futureintervention studies with larger sample size are necessary to furtherinvestigate this promising therapeutic effect.
References:
1. Wierenga CE, Hays CC, ZlatarZZ. Cerebral blood flow measured by arterial spin labeling MRI as a preclinicalmarker of alzheimer's disease. Journal of Alzheimer's Disease. 2014. p. S411-9.
2. Haast RAM,Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function.ProstaglandinsLeukotrienes and Essential Fatty Acids. 2015. p. 3-14.

PS01-049 **Cerebral blood flow in patients with white matter hyperintensities and effect of co-variates**
Yulu Shi, United Kingdom
Objectives: White matter hyperintensities (WMH) are highly prevalent in older people and are associated with increased risk of stroke and dementia. It has been hypothesized that reduced cerebral blood flow (CBF) causes WMH, however previous studies did not account for age and brain atrophy [1]. In this cross-sectional study, we investigated the relationship between CBF and WMH after adjustment for confounders.
Methods: We scanned 60 patients with mild ischemic stroke and WMH in a 1.5T GE scanner. CBF was measured using phase-contrast MRI, calculating total CBF from blood flow in internal carotid and vertebral arteries. WMH, brain volume, and intra-cranial volume (ICV) were computed from validated tissue processing methods from structural MRI. We performed linear regression to investigate the relationships between variables. WMH/ICV ratio was log-transformed in all regression models.
Results: Complete CBF and WMH data were obtained from 56/60 patients (mean age 67.95±8.69 yrs; 40 male). Mean total CBF was 654.32±113.00 ml/min or 60.17±9.52 ml/min per 100 ml of brain volume. The median WMH volume was 10.74ml (range 1.40-74.97 ml), representing median WMH/ICV 0.74 % (range 0.11-5.17 %). In univariate analysis, higher WMH/ICV ratio was significantly related to lower total CBF (ml/min) (β=-0.268, P=0.046), but the relationship weakened using normalised CBF to brain volume data (β=-0.248, P=0.065). After adjustment for age, gender and brain volume/ICV ratio, the relationship between WMH/ICV and CBF further decreased (β=-0.127, P=0.306), whereas more WMH remained associated with older age (β=0.540, P< 0.001).
Conclusions: WMH seemed to be more related to older age in cross-sectional analysis, rather than lower CBF per 100ml of brain volume. Future studies should seek alternative mechanisms for WMH, such as altered dynamic function of cerebral small vessels.
References: [1]Shi Y, *et al.* Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. *JCBFM* 2016;38:1653-1667.

03.04.2017

Symposium session
16:00 – 17:30 Hörsaal A

In Vivo Veritas: a tribute to Louis Sokoloff. Use of quantitative biochemical techniques to explore roles of lactate in vivo

Fahmeed Hyder, United States

SY08-2 **Aerobic glycolysis in resting brain: Quantitative analysis of oxygen-glucose indices as functions of age in humans** 16:05 – 16:25

Albert Gjedde, Denmark

Louis Sokoloff conceived of the 2DG method as a measure of the rate of glucose phosphorylation. Sokoloff based the method on the insight that hexokinase performs the phosphorylation but the product is stuck in the brain as a marker of the activity of hexokinase.

Aerobic glycolysis refers to the observation in adequately oxygenated tissue that not all glucose-6-phosphate undergoes full oxidation to CO_2 but either remains as glucose metabolites, or leaves the tissue as glucose or as a metabolite other than CO_2. For the brain, the convention holds that lactate efflux from brain tissue to the circulation is the driver of the loss of glucose moieties when near-equilibrium LDH converts pyruvate to lactate as rapidly as lactate is transported from brain.

Recent authors now limit the concept of aerobic glycolysis to the production of glucose-6-phosphate metabolites other than CO_2 and lactate, i.e., to metabolites that remain in brain. They argue that the quantity of lactate that leaves the brain is minuscule, and that aerobic glycolysis contributes to structural expansion of the brain by supplying masses of glucose metabolites that in theory would weigh more by orders of magnitude than the actual changes of brain weight. This discrepancy is particularly evident during the expansion of the brain in childhood when the glucose moieties engage in the process of "neoteny" of children's brains.

Here, the speaker will address the issue of the relative metabolic fates of glucose-6-phosphate, as measured with the tracer deoxyglucose analog fluorodeoxyglucose in human brain. The speaker will test the hypothesis of aerobic glycolysis as the major contributor to brain developmental plasticity in children, and he will show that the test fails, inasmuch as the major contributor to aerobic glycolysis by far is the production of lactate, possibly assisted by loss of glucose regenerated by the action of glucose-6-phosphatase.

SY08-3 **Aerobic glycolysis in activated brain: Catecholamines, astrocytes, and lactate efflux** 16:25 – 16:45

Gerald Dienel, United States

The magnitude of aerobicglycolysis, defined as the disproportionate utilization of glucose (CMR_{glc})or total carbohydrate ($CMR_{glc+0.5lac}$) compared with oxygen (CMR_{O2}),increases (i.e., $CMR_{O2}/CMR_{carbohydrate}$ falls) duringbrain activation and exercise in normal subjects even though oxygen level anddelivery are normal. Manifestation of aerobic glycolysis under many conditionsindicates that any astrocyte-neuron lactate shuttling is negligible becauselactate oxidation requires a proportionate increase in CMR_{O2} withCMR_{glc}. Greater flux of glucose into three metabolic pathways contributesto aerobic glycolysis in activated, awake rats, with glycolysis and lactaterelease having the largest contribution. Glucose phosphorylation rises inexcess of oxidative metabolism, causing 2-3-fold increases in brain lactatelevel and stimulating lactate efflux from brain. Pentose shunt flux also rises,generating CO_2 without oxygen consumption. Consumption of glycogen, increasedglycogen turnover, and prolonged glycogen re-synthesis during recovery contributeto aerobic glycolysis. The cellular basis of aerobic glycolysis is unknown, butastrocytes are poised to be major contributors, in part, because they containglycogen and they rapidly take up lactate from extracellular fluid and

disperselactate via gap junctional trafficking, facilitating its discharge from endfeet to lymphatic drainageand blood. Also, astrocytes express α- and β-adrenergic receptors (ARs), and noradrenalinecan influence glucose and glycogen metabolism via different signaling pathways.Pre-treatment of humans and rats prior to activation with propranolol, anon-specific β-AR blocker, prevents aerobic glycolysis, whereas metoprolol (a specificβ_1-blocker that would inhibit glycogenolysis) doesnot, implicating β_2-ARs as mediators ofaerobic glycolysis. Propranolol Â´re-balancesÂ´ CMR_{O2}-CMR_{glc}stoichiometry by reducing effects of catecholamines on β-ARs without affecting their actions of α-ARs, thereby decreasing carbohydrateutilization more than oxygen consumption, causing the CMR_{O2}/CMR_{glc}ratio to rise. Predominant regulation of aerobic glycolysis by catecholaminesrules out a major contribution of any glutamate-induced glycolysis in astrocytesand astrocyte-neuron lactate shuttling to energetics of brain activation.

SY08-4 **Lactate shuttling: Modeling and measuring astrocyte neuron interactions** 16:45 – 17:05

Douglas Rothman, United States

Astrocytes play multiple key metabolic roles for supporting neuronal functions such as glutamate and GABA neurotransmission. There has been great interest over the last two decades tin he potential role of astrocytes in providing lactate as fuel to support the activity dependent energy consumption in neurons, often called the astrocyte neuron lactate shuttle (ANLS). Most of the evidence for or against the ANLS model has been derived from studies of isolated astrocytic cell cultures. In this presentation the focus will instead be on the in vivo metabolic evidence for the significance of this pathway.

The presentation will be in four parts:

I) The in vivo coupling between glutamate neurotransmission and neuroenergetics

II) ANLS and non ANLS models to explain this coupling.

III) Capacity in vivo of neurons to take up exogenous lactate.

IV) In vivo studies directly testing the ANLS hypothesis via measurement of glial and neuronal glucose uptake during functional activity.

It is concluded that based on the in vivo data it is unlikely that the ANLS is normally a significant contributor to neuroenergetics . However an alternate model will be presented that an ANLS mechanism using glycogen could potentially occur under extreme circumstances of substrate deprivation, and in doing so set the stoichiometry between functional neuronal glucose oxidation and glutamate/glutamine cycling.

References:

Dienel G et al. Microdialysate concentration changes do not provide sufficient information to evaluate metabolic effects of lactate supplementation in brain injured patients. J. Cereb. Blood Flow Metab. 36 (11), 1844-1864, 2016.

Patel AB et al. Direct evidence for activity dependent glucose phosphorylation in neurons, implications for the astrocyte to neuron lactate shuttle. Proc. Nat. Acad. Sci. (USA). 111(14): 5385-5390, 2014.

Hyder F et al. Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. Journal of Cerebral Blood Flow & Metabolism. 26(7):865-77, 2006.

SY08-5 **Bedside evaluation of cerebral energy status and lactate supplementation after brain injury** 17:05 – 17:25

Carl-Henrik Nordström, Sweden

Microdialysis offers the possibility of obtaining information regarding the chemical composition of cerebral interstitial fluid during neurocritical care. The biochemical analyses routinely displayed bedside include glucose, pyruvate, lactate, glutamate and glycerol. Due to various technical limitations (*i.e.* relative recovery during microdialysis, imprecision of the biochemical analyses) the data obtained do usually not give the true interstitial concentrations of the variables. The routine analyses have the accuracy and precision required for clinical application in neurointensive care but the limitations must be taken into account when the data are used for interpretation of pathophysiological mechanisms.

During clinical intracerebral microdialysis, an increase of the LP ratio is considered

as the most sensitive indicator of jeopardized cerebral energy metabolism. During neurocritical care, an increase of the LP ratio is usually caused by insufficient tissue oxygenation (e.g. arterial hypoxia, cerebral ischemia) and/or mitochondrial dysfunction. The two conditions can be separated at the bedside by simultaneous monitoring of the LP ratio and brain tissue oxygenation ($PbtO_2$). If under clinical conditions microdialysis is used alone, a separation between the two conditions may still be obtained. In cerebral ischemia, the increase in LP ratio occurs at a pronounced decrease in pyruvate level, while in mitochondrial dysfunction, the increase in LP ratio is observed at a normal or increased concentration of pyruvate. An increase in LP ratio is always caused by insufficient oxidative metabolism. Decreased delivery of substrate does not, in itself, cause an increase in LP ratio. Even when blood glucose is reduced to such a low level that cerebral energy metabolism collapses, LP ratio remains normal. Accordingly, in a clinical situation of increased cerebral LP ratio at a low cerebral glucose concentration, the metabolic pattern is caused by insufficient oxidative metabolism. Efforts to improve cerebral energy state by delivering lactate in this situation are futile and erroneous.

SY08-6 **Discussion** 17:25 – 17:30