31. Energy Metabolism of the Brain

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first draft of outline 7/03

Introduction

- The brain consumes about one-fifth of total body oxygen utilization
- The main energy-demanding functions of the brain are those of ion flux related to excitation and conduction
- Brain metabolism is complex-- Neurons and glia are partners in brain function

Substrates of Cerebral Metabolism

- Substrates enter the brain from the blood
- The blood-brain barrier has specific transporters for the uptake of nutrients including glucose
  - Transporters for glucose and monocarboxylic acids are developmentally regulated
- Metabolism and substrate utlilzation changes during development
- ketone bodies and lactate are important substrates for energy and synthesis of lipids and amino acids in developing brain
  - glucose is also needed by developing brain
- glucose utilization is obligatory for adult brain

Age and Development Influence Cerebral Energy metabolism

- The rate and pathways of metabolism change during development
  - Metabolic rate increases during early development
  - Metabolic rate declines and plateaus after maturation
    - Tissue pathology, but not ageing, produces secondary changes in metabolic rate

Regulation of Cerebral Metabolic Rate

- Continuous cerebral circulation is absolutely required to provide sufficient oxygen
- Cerebral metabolic rate differs regionally

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Intermediary Metabolism

- Compartmentation greatly influences metabolism
- **Figure** of compartmentation
  -- several important enzymes are found only in astrocytes, e.g. pyruvate carboxylase and glutamine synthetase
  -- transporters for glucose and monocarboxylic acids are differentially distributed on brain cells (**Figure *of distribution of glucose and MCT transporters -- from Vannucci and Simpson if possible)***
  -- glutamate in brain is compartmented into separate pools
  -- Glycogen is a dynamic but limited energy store localized in astrocytes in brain glycogen is broken down to lactate, not glucose

- There is a continuous dynamic exchange of compounds neurons and glial cells called "metabolic trafficking"
  - Glutamate from neurons is converted to glutamine by astrocytes and released
  - Uptake of neurotransmitters influences astrocyte metabolism

- ATP production in brain is highly regulated
  - Brain glycolysis is regulated mainly by hexokinase and phosphofructokinase
  - The pyruvate dehydrogenase complex plays a key role in regulating oxidation
  - Energy output and oxygen consumption are associated with high rates of enzyme activity in the Krebs cycle
  - Substrates other than glucose provide energy for brain cells (e.g. glutamate, glutamine, lactate, fatty acids, ketone bodies)

- The malate/aspartate shuttle has a key role in brain metabolism
  - Essential for transferring reducing equivalents from the cytosol to the mitochondria
  - Links energy metabolism and neurotransmitter biosynthesis

- The pentose shunt, also termed hexose monophosphate pathway, is active in brain
  - The NADPH produced by this pathway is important for lipid biosynthesis and maintaining reduced glutathione

- The pyruvate recycling pathway can maintain TCA cycle activity when glucose is low

- Mitochondrial heterogeneity—many enzymes and components of oxidative phosphorylation are differentially distributed in neuronal and glial mitochondria

- Current controversies -- mention Lac shuttle – [where to put this??]

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How Brain Metabolism is Studied

- **In Vivo** – Many techniques can be used to study or determine brain metabolism in vivo
  - Clinical and research -- cerebral metabolic rate is determined locally by functional activity in discrete regions
    - Oxygen utilization in the cortex is measured by polarographic techniques
    - PET scanning measures regional uptake of glucose and other substrates by brain
    - NMR spectroscopy is an important tool for studying brain metabolism
      - fMRI is used to study regional metabolism
      - ^{31}P-NMR is used to determine ATP and high energy phosphates
      - ^{13}C-NMR is used to determine pathways of substrate metabolism and neuronal/glial trafficking
  - Primarily research
    - microdialysis and microelectrodes are used to determine the concentration of compounds in the extracellular space in brain

  - Damaged or abnormal areas of brain exhibit altered metabolism

- **In Vitro –** in vitro studies are not complicated by blood flow and hormonal influences
  - Preparations
    - Primary cultures of brain cells are an important tool for studying differences in metabolism of neurons and glia
    - Brain slices and cocultures are used to study metabolism and neuronal/glial interactions
    - Isolated mitochondria are used for enzyme and metabolic studies
    - Autoradiography is used to study regional uptake of substrates
- NMR spectroscopy has led to major advances in our understanding of brain metabolism

Cerebral Energy Metabolism in Physiological and Pathological States

- Normal metabolism depends on circulation for oxygen and glucose
  - blood and cerebral spinal fluid chemical changes can alter metabolism
- Anesthesia, coma and systemic metabolic disease depress brain metabolism
- Damaged or abnormal areas of brain exhibit altered metabolism in vivo and in vitro
- Alterations in energy metabolism can be due to changes in neurons, changes in glia, alterations in neuronal/glial trafficking
- Compromised energy metabolism can result in neurodegeneration

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Tentative Figures (not final or complete)

1—schematic of neuronal/glial trafficking
2--figure of distribution of glucose and MCT transporters on BBB and brain cells
3--Metabolism -- glycolysis, TCA cycle
4--compartmentation of metabolism (could be combined with 1)
5--^{31}P-NMR spectra of high energy metabolites (source? Can we get permission for literature figures?)
6a & 6b --^{13}C-NMR spectra of whole brain [acetate and glucose; separate or together?] & labeling pattern figure
7a & 7b—^{13}C-NMR spectra of brain cells [media and PCA extract separately—either astrocytes or neurons]

Tables (not final or complete)

Table 31-1 Cerebral Blood Flow and metabolic rate in a normal young adult man (possibly keep)
1--Table of rates of regional glucose utilization (to show differences)
2--Table of rates metabolism of substrates by brain cells [lit data; Edmond, McKenna, Schousboe, etc)
3--Table showing neuronal vs glial distribution of electron transport chain components (from John Clark's work)
4--Table of compounds labeled in NMR spectra of brain (to go with spectra in 6a)
5-- Table of compounds labeled in NMR spectra of brain cells (to go with spectra in 7a & b)
Table 31-6. Cerebral Blood Flow and Oxygen Consumption in Human from Childhood to Old Age and Senility (possibly keep and update if needed)

Questions

Do we need a PET, of FMRI image or will imaging chapter take care of those?
How much of blood flow will be encompassed in the imaging chapter?

How much to say about currently controversial areas e.g. ANSLH

Things in current chapter that will be deleted: (tentative)

Table 31-2 Representative values for local cerebral glucose utilization in the normal conscious albino rat and monkey (umol/100g/min)
Table 31-3. Relationship Between cerebral oxygen consumption and glucose utilization in a normal young adult man
Table 31-4. Effects of Insulin hypoglycemia on cerebral circulation and metabolism in humans
Table 31-5. Effectiveness of various substances in preventing or reversing the effects of hypoglycemia or glucose deprivation on cerebral function and metabolism
Table 31-7. Relationship Between Level of Consciousness and Cerebral MetabolicRate
Table 31-8. Cerebral Blood flow and metabolic rate in schizophrenia and in normal young men during LSD-induced psychotomimetic state

Figure 31-1. Glycogen metabolism
Figure 31-2. Glycolysis in brain
Figure 31-3. Theoretical basis of
Figure 31-4. Autoradiograms of coronal
Figure 31-5. Local glucose utilization
Figure 31-6. Effects of Electrical

32: Hypoxic-Ischemic Brain Injury and Oxidative Stress

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Introduction

Hypoxia-ischemia and brain infarction.

1 Rapid energy failure causes disruption of ionic homeostasis and accumulation of extracellular neurotransmitters.

2. Focal and global ischemia produce different distributions of injury.

3. The "selective vulnerability" of specific populations of neurons or glial cells is not explained by vascular distribution.

Microvascular injury in hypoxia-ischemia

1. Hypoxia-ischemia disrupts the blood-brain barrier and damages endothelial cells.

2. Metalloproteinases may be involved in cerebrovascular injury

3. Consequent edema and secondary ischemia can produce further brain damage.

4. Role of aqueporins in brain edema

Excitotoxic injury in hypoxia-ischemia

1. Both NMDA and AMPA/kainate receptors contribute to excitotoxic degeneration of neurons and glia.

2. Excitotoxicity leads to increased intracellular Ca^{2+} and Zn^{2+}, which can activate toxic intracellular pathways.

Ischemic Apoptosis

1. Hypoxia-ischemia may initiate apoptosis in parallel with excitotoxicity.

2. Triggers of ischemic apoptosis may include decreased supply or sensitivity to neurotrophins, oxidative stress, or exposure to inflammatory cytokines.

Reactive oxygen and nitrogen species in hypoxia-ischemia

1. Reactive oxygen species (ROS) and nitrogen species (RNS) are required intermediates in many biological reactions, but may damage macromolecules

2. ROS/RNS generated during ischemia-reperfusion injury contribute to injury and may compromise brain metabolism

3. Brain antioxidant defenses modify ischemia-reperfusion injury.

Neuroprotective strategies for hypoxic-ischemic injury

1. Endogenous protective programs may include ischemic preconditioning and the heat shock response

2. Efficacy of thrombolytics and neuroprotective drugs in hypoxia-ischemia

33. Lipid messengers in cell function and diseases

Nicolas G. Bazan

1. Introduction

A. ***Develop the concept that synaptic membranes as well as other cell membranes (in neurons, astrocytes, brain microvasculature,/infiltrating inflammatory cells, etc) contain specific phospholipids that are reservoirs of lipid messengers.***

B. Specific signals (e.g., neurotransmitters , neurotrophic factors) activate enzymes that cleave the reservoirs releasing the messengers.

C. Remodeling of polyunsaturated fatty acyl chains in membrane phospholipids. Signaling through lipid messengers that regulate cell functions and the overactivation of some of these events in pathological conditions.

2. Phospholipases A2

A. cPLA2

B. sPLA2

a. Multiple isoforms

b. The enzyme an intercellular messenger by itself

C. iPLA2

3. Phospholipase C

4. Phospholipase D

5. Diacylglycerol- and monoacylglycerol- lipases

6. Diacylglycerol kinases

A. Multiple isoformes

B. Brain specific diacylglycerol kinase epsilon

7. Cyclooxygenases and lipoxigenases

8. Arachidonic acid

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9. Synaptic activation, ischemia or seizures stimulate phospholipases

A. The accumulation of arachidonic, docosahexaenoic and of other fatty acids.
B. Diacylglycerol release

10. Eicosanoids

A. Prostaglandins and related bioactive lipids
B. Lipoxygenase messengers
C. Lipoxins
D. Leukotrienes
E. Epoxi- and hydroxyl-modified arachidonIc acids

11. Cyclooxygenase 2-generated prostaglandin E2 modulates postsynaptic membrane excitability and long -term synaptic plasticity.

A. Prostaglandins synthesis and release from astrocytes
B. Prostaglandins synthesis and release from neurons

12. Ischemia-reperfusion and proinflammatory pathologies promote the accumulation of oxygenated lipid messengers as well as of lipid peroxidation products.

13. Endocannabinoids

A. Anandamide (N-arachidonoylethanolamine)
B. 2-arachidonoyl-glycerol, 2-arachidonoyl-glyceryl ether and virodhamine.
C. Cannabinoid receptors

14. Docosahexaenoic acid ***Develop the theme that docosahexaenoic acid, derived from the essential fatty acid linoleic acid, is the only polyunsaturated exclusively concentrated in the central nervous system.***

A. Synaptic membranes
B. Photoreceptors
C. The liver supply of essential fatty acids to the brain and retina; transport, uptake and retention
D. Significance in retinal degenerations
E. Enzyme-mediated synthesis of docosanoids
   a. Docosanoids in brain ischemia-reperfusion
   b. Docosanoids and leukocyte infiltration in experimental stroke
   c. Docosanoids and proinflammatory gene expression
   d. Significance of docosahexaenoic acid in experimental stroke and neuroprotection
F. Peroxidation and oxidative stress
G. Neuroprostanes

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34. Hypoxic-Ischemic Brain Injury and Oxidative Stress

Laura L. Dugan, Kevin L. Quick, Jeong Sook Kim-Han

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2. ROS/RNS generated during ischemia-reperfusion injury contribute to injury.

3. There are multiple sources of ROS/RNS.

4. Brain metabolism may be compromised by ROS/RNS.

5. Brain antioxidant defenses modify ischemia-reperfusion injury.

Conclusions

38. METABOLIC ENCEPHALOPATHIES

Roger F. Butterworth

INTRODUCTION

ELECTROLYTE IMBALANCE

- Hyponatremia
- Central pontine myelinolysis is an iatrogenic disorder caused by too rapid correction of hyponatremia
- Hypernatremia

VITAMIN DEFICIENCIES

- Thiamine deficiency (Wernicke-Korsakoff syndrome)
- The "biochemical" (reversible) lesion in thiamine deficiency results from the consequences of decreased brain pyruvate oxidation.
- The thiamine-dependent enzyme α-ketoglutarate dehydrogenase is sensitive to oxidative stress
- Pyridoxine deficiency
- Folate/vitamin B_{12} deficiency
- Nicotine acid deficiency

METABOLIC ENCEPHALOPATHIES DUE TO SYSTEMIC DISEASE

- HEPATIC ENCEPHALOPATHY
    - Liver failure leads to the accumulation of toxic substances (ammonia, manganese) in the brain
    - Hepatic encephalopathy is a disorder of multiple neurotransmitters

- UREMIC/DIALYSIS ENCEPHALOPATHIES
    - Uremia results in alterations of the blood brain barrier
    - Aluminium neurotoxicity plays a role in the pathogenesis of dialysis encephalopathy

- DIABETIC/INSULIN COMA

REFERENCES

35. Apoptosis and Necrosis

Mark P. Mattson and Nicolas Bazan