Fetal and neonatal Brain development: histology and biochemistry

- Early neuronal migration
- Late neuronal migration
- Cerebral blood flow
- Autoregulation of CBF
- Cerebral metabolism: $CM$
- Autoregulation of CM
- Focus on neurons
- Focus on glial cells
- Clinical examinations
- Imaging

40% glial cells, 4% neurons, 4% blood, 10% CSF, 35% ECF, 10% variance
FIGURE 3.11 Schematic representation of the mechanism for glutamate-induced glycolysis in astrocytes during physiological activation. At glutamatergic synapses, presynaptically released glutamate depolarizes postsynaptic neurons by acting at specific receptor subtypes. The action of glutamate is terminated by an efficient glutamate uptake system located primarily in astrocytes. Glutamate is cotransported with Na⁺, resulting in an increase in the intracellular concentration of Na⁺, leading to activation of the astrocyte Na⁺/K⁺-ATPase. Excitation of the Na⁺/K⁺-ATPase stimulates glycolysis (i.e., glucose utilization and lactate production). The stoichiometry of this process is such that for one glutamate molecule taken up by two to three Na⁺ ions, one glucose molecule enters astrocytes, two ATP molecules are produced through glycolysis, and two lactate molecules are released. Within the astrocyte, one ATP fuels one “turn of the pump,” while the other provides the energy needed to convert glutamate to glutamine by glutamine synthase (see Fig. 3.13). Lactate, once released by astrocytes, can be taken up by neurons and serve as an adequate energy substrate. (For graphic clarity only, lactate uptake into presynaptic terminals is indicated. However, this process could also take place at the postsynaptic neuron.) In accord with recent evidence, glutamate receptors are also shown on astrocytes. This model, which summarizes in vitro experimental evidence indicating glutamate-induced glycolysis, is taken to show cellular and molecular events occurring during activation of a given cortical area (arrow labeled A, excitation). Direct glucose uptake into neurons under basal conditions is also shown (arrow labeled B, basal conditions). Pyr, pyruvate; Lac, lactate; Gin, glutamine; G, G protein; PGK, phosphoglucomutase. Modified from Pellecini and Magistrati (1994).

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**FIGURE 1.21** Microvasculature of the human neocortex. (A) Primary visual cortex (area 17). Note the presence of segments of deep penetrating arteries that have a larger diameter than the microvessels and run from the pial surface to the deep cortical layers, as well as the high density of microvessels in the middle layer (layers IVB and IVCb). (B) Prefrontal cortex (area 9). Cortical layers are indicated by Roman numerals. The microvessels are stained using an antibody against heparan sulfate proteoglycan core protein, a component of the extracellular matrix.
FIGURE 1.16 Arrangement of astrocytes in human cerebellar cortex. The Bergmann glial cells are in red, the protoplasmic astrocytes are in green, and the fibrous astrocytes are in blue.

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Importance of histology

- In cellular migration:
  - in brain:
  - in cerebellum:
- In cellular plasticity:
  - in dendrites and axons;
  - in hippocampus;
FIGURE 3.14 The astrocyte–neuron metabolic unit. Glutamatergic terminals and the astrocytic processes that surround them can be viewed as a highly specialized metabolic unit in which the activation signal (glutamate) is furnished by the neuron to the astrocyte, whereas the astrocyte provides the precursors needed to maintain the neurotransmitter pool (glutamine, lactate, alanine), as well as the energy substrate (lactate). AP, astrocyte process.

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The concept of neurone-glial cells association

Oligodendrocytes:
Perineuronal;

Astrocytes:
perivascular,
in White and grey matter

Microcytes:
travellers

Layers 1, 2 and 3 for intra-cortical associative relationships
1, 4, 5, 6 for projective intra-cortical and subcortical relationships

Radial cells
Illustration of neuronal migration and plasticity

Before finding target, hypersensitive period To NMDA

neurones en migration...
The blood-brain barrier

- Brain cells: neurons, astrocytes, microcytes, oligodendrocytes;
- Microcirculation;
- Ependyma and villi;
- Arachnoids;
FIGURE 3.9 Cellular distribution of the principal glucose transporters in the nervous system.

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The intertissular metabolic integration

- **About nutritional needs and storages:**
  - aminoacids, fat and Carbohydrates;
  - flow autoregulation;
- **About cerebral growth:**
  - in preterms;
  - in case of retarded growth;
- **About muscles growth:**
  - in preterms;
  - in case of retarded growth;

15 % body mass; 60 % BMR

24 % body mass
Development of important structures

- **Those controlling senses:** vision, hearing, smelling, tasting, touch-feeling;
- **Those controlling movements:** extra-pyramidal and pyramidal tracts; basal ganglia and cerebellum.
- **Those controlling autonomous functions:** circulation, respiration, prokinesis, …
- **Those controlling endocrine functions:** neuroendocrinology.
- **Those controlling memory**
FIGURE 18.2 Schematic of a transverse hippocampal brain slice preparation from the rat. Two extracellular stimulating electrodes are used to activate two nonoverlapping inputs to pyramidal neurons of the CA1 region of the hippocampus. Both inputs consisted of axons of the Schaffer collateral/commissural (Sch/com) system. By suitably adjusting the current intensity delivered to the stimulating electrodes, different numbers of Sch/com axons can be activated. In this way, one stimulating electrode was made to produce a weak postsynaptic response and the other to produce a strong postsynaptic response. Sometimes three or more stimulating electrodes are used. Also illustrated is an extracellular recording electrode placed in the stratum radiatum (the projection zone of the Sch/com inputs) and an intracellular recording electrode in the stratum pyramidale (the cell body layer). Also indicated is the mossy fiber projection from the granule cells of the dentate gyrus (DG) to the pyramidal neurons of the CA3 region. Adapted from Barrionuevo and Brown (1983).

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FIGURE 9.2 Schematic representation of the life cycle of a classic neurotransmitter. After accumulation of a precursor amino acid (X) into the neuron (step 1), the amino acid precursor is sequentially metabolized (step 2) to yield the mature transmitter (ZZ). The transmitter is then accumulated into vesicles by the vesicular transporter (step 3), where it is poised for release and protected from degradation. The released transmitter can interact with postsynaptic receptors (step 4) or autoreceptors (step 5) that regulate transmitter release, synthesis, or firing rate. Transmitter actions are terminated by means of a high-affinity membrane transporter (step 6) that is usually associated with the neuron that released the transmitter. Alternatively, the actions of the transmitter may be terminated by means of diffusion (step 7) or by accumulation into glia through a membrane transporter (step 8). When the transmitter is taken up by the neuron, it is subject to metabolic inactivation (step 9).

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Central role of glucose for energy an synthesis

- ATP and 5-Pentose;
- In- and out-cells composition
- neurotransmission
- Defenses against FR and EAA
- BMR
- Muscles (FFA) and intestines (glutamine and KB) have alternatives
FIGURE 3.13 Metabolic intermediates are released by astrocytes to regenerate the glutamate neurotransmitter pool in neurons. Glutamine, formed from glutamate in a reaction catalyzed by glutamine synthase (GS), is released by astrocytes and taken up by neurons, which convert it into glutamate under the action of glutaminase. GS is an enzyme selectively localized in astrocytes. This metabolic cycle is referred to as the glutamate–glutamine shuttle. Other, quantitatively less important sources of neuronal glutamate are lactate, alanine, and α-ketoglutarate (α-KG). In astrocytes, glutamate is synthesized de novo from α-KG in a reaction catalyzed by glutamate dehydrogenase (GDH). The carbon backbone of glutamate is exported by astrocytes after conversion into glutamine under the action of GS; the conversion of leucine into α-ketoisocaproate (α-KIC), catalyzed by leucine transaminase (LT), provides the amino group for the synthesis of glutamine from glutamate. The carbons “lost” from the TCA cycle as α-KG is converted into glutamate are replenished by oxaloacetate (OxA) formed from pyruvate in a reaction catalyzed by pyruvate carboxylase (PC), another astrocyte-specific enzyme.

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Glucose and O₂ requirements in the distressed brain

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<th>Cbf ml/100g/min</th>
<th>[ aG ] -&gt; I</th>
<th>[ aG ] -&gt; W</th>
<th>[ aO₂ ] -&gt; I</th>
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<td>2</td>
<td>82</td>
<td>143</td>
<td>28#</td>
<td>62#</td>
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</tbody>
</table>
FIGURE 3.7 Energy budget for the rodent central cortex (Attwell and Laughlin, 2001). Relative rates of ATP consumption by resting neurons and glia (left). Relative cost of the various processes associated with a firing rate of 4 Hz for a glutamatergic pyramidal neuron. Modified from Laughlin and Attwell in Frackowiak et al. (2001).

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Glucose and energy in cells: cytoplasm and mitochondria

**In normal cell:**

\[ \text{G + O}_2 \rightarrow \text{ATP + CO}_2 + \text{H}_2\text{O} \]

Free radicals \rightarrow coupled radicals

**In cell with mitochondrial impairment:**

\[ \text{G + O}_2 \rightarrow \text{ATP + CO}_2 + \text{lactic acid} \]

hypoxia \rightarrow \text{Loss of energy and Electrolytes disturbances}

reoxygenation \rightarrow Free radicals

> 95 %
FIGURE 3.6 Enzymatic reactions for scavenging reactive oxygen species (ROS). The toxic superoxide anion (O$_2^-$) formed by a variety of physiological reactions, including oxidative phosphorylation, is scavenged by superoxide dismutase, which converts the superoxide anion into hydrogen peroxide (H$_2$O$_2$) and molecular oxygen. Glutathione peroxidase converts the still toxic hydrogen peroxide into water; reduced glutathione (GSH) is required for this reaction, in which it is converted into its oxidized form (GSSG). GSH is regenerated through the action of glutathione reductase, a reaction requiring NADPH.

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FIGURE 1.18 Astrocytes (in orange) are depicted in situ in schematic relationship with other cell types with which they are known to interact. Astrocytes send processes that surround neurons and synapses, blood vessels, and the region of the node of Ranvier and extend to the ependyma as well as to the pia mater, where they form the glia limitans.

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FIGURE 1.20 Activation of microglial cells in a tissue section from human brain. Resting microglia in normal brain (A). Activated microglia in diseased cerebral cortex (B) have thicker processes and larger cell bodies. In regions of frank pathology (C) microglia transform into phagocytic macrophages, which can also develop from circulating monocytes that enter the brain. Arrow in B indicates rod cell. Sections stained with antibody to ferritin. Bar = 40 μm.

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FIGURE 16.23
Principal components of the various parts of the internal capsule, as seen in a horizontal section (A) and in the figure. The thalamic cell bodies indicated schematically in B would actually be on the other side of the internal capsule in both parts of the figure. For example, the anterior nucleus and the pulvinar are not present in the plane of bodies are indicated; neither claustrum nor auditory cortex is present in the dissection shown in B, so no points. (A modified from Nolte J. The human brain in photograph and diagram, St. Louis. 1975, Mosby; B modified from Atlas of the human brain, Boston. 1960, Little. Brown & Co.)
About the Structures controlling the movements

- Extrapyramidal tracts;
- Pyramidal tracts;
- Basal ganglia;
- Oculomotor fibers;
- Reticulated structures and brain stem;
- Peripheral nerves;
- Muscles;

Thalamus, the planner by Dopamine (Na+, H+, Cl-)

Professeur Oreste Battisti, Ulg
Structures controlling the senses

- Smelling;
- Tasting;
- Touch feeling;
- Hearing;
- Vision;

hippocampus and amygdala: memory
Structures controlling the autonomous nervous system and the movements

- Heart rate;
- Blood pressure;
- O2 consumption;
- Heat control;
- Respiration;
- Prokinesis and secretion;
- Voluntary and involuntary movements;

Variability of inputs

→ globus pallidus → thalamus ← cerebellum

Fig. 182. — Diagramme du système cortico-sous-cortical
Cerebral blood flow and metabolic autoregulation loss or absence

- **CBF absent if:**
  - respiratory distress;
  - circulatory distress;
  - hypoglycemia;
  - CNS infection;
  - brain trauma;
- **Loosing the independence to:**
  - 1° Systolic blood pressure;
  - 2° CO2 pressure;
  - 3° O2 content;
Acute Markers of cerebral impairment...

- **Clinically:**
  changes of movements (→ convulsions), in tonus, in parameters depending of the autonomous nervous system: heart rate, blood pressure, respiratory rate, temperature, peristaltism, mucosal secretions...

- **Biochemically:**
  dismanagement of glycemia, acidosis, hyper NH₃, increase of certain aminoacids, of uric acid, of hypoxanthine, of CKB enzyme, or free radicals,…
About the periods of sleep

- **REM-periods**: under adrenergic control; synthesis of proteins and neurotransmitters; high metabolic rate. Correlation with growth.

- **Non REM-periods**: under vagal control; pauses in synthesis; lower metabolic rate.
Endogenous opioids, catecholamines and neurotransmission

- Massage:
  - of the body;
  - of the face;
- Eating and swallowing:
- Relationships with corticoids, melatonin, PMC;
- Understanding the changing physiology of clinical examination: subcortical to cortical, extrapyramidal to pyramidal, multi-unit to mono-fibrillar unit;
- The archaic reflexes;
Cerebral lesions in the neonates and their « repair »

- White matter damage;
- Hemorrhagic leukomalacia;
- Intra/periventricular; hemorrhage;
- Arachnoid hemorrhage;
- Pericerebellar hemorrhage;
- Occlusive vascular disorder;
- Cerebral edema;
- Meningitis;
- Encephalitis;
- Hydrocephalus, ventricular dilation;
- Porencephalus;
Investigations in neonatal neurology

• Clinical examination;
• Ultrasounds (with Doppler);
• Electrophysiology: mainly EEG;
• MRI: anatomy and spectroscopy;
• NIRS: muscles and brain;
• Biology: blood, CSF;
During the hospital stay

• Cerebral metabolic and blood flow parameters and autoregulation
• Importance of ultrasounds and EEG; MRI in specific technical conditions
• Pay attention to drugs such as steroids, morphines, midazolam, xylocaine, NO, management of pain
• To inflammation, alcohol, methadone, cocaine, heroine, nicotine, repetitive pain, sleep-awake cycling
• Special conditions for IDM, IUGR, PT < 30 weeks,
In the follow-up period

Volumes, myelin, language, vision, attention, memory

- **32 weeks of fetal life**: a cross-line period
- Neonatal medicine has to be extended till 4 months after term;
- Importance of « MRI »: 5 months, 7-8 yrs, 14-18 yrs;
- Neurophysiology studies till
- Disturbances in neurotransmitters’ synthesis and balance can emerge in babies born before 32 weeks
- Assessment of language, memory, attention

Internal capsule, optic radiations, corpus callosum, left temporal lobe, cerebellum

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