CHALLENGES IN ANESTHETIC MANAGEMENT OF EPILEPTIC CHILD

Essay

Submitted for fulfillment of Master Degree in Anaesthesiology

By

Beshoy Nabil MaoudFam

M.B.B.CH

Under supervision of

Prof. Dr. MOHAMED ISMAEIL EL-SAIEDI

Prof of Anesthesia and Intensive care
Faculty of medicine - Ain shams university

Dr. SALWA OMAR EL-KHATTAB

Assist. Prof of Anesthesia and Intensive care
Faculty of medicine - Ainshams university

Dr. HANY AHMED ABD EL-KADER

Lecturer of Anesthesia and Intensive care
Faculty of medicine - Ain shams university

Faculty of Medicine
Ain Shams University

2012

Acknowledgement *

First and foremost I thank **ALLAH** for every thing and especially for my steady steps I have been taking in my career.

I would like to express my most sincere thanks and deepest gratitude to **Prof.Dr. Mohamed Ismaeil El-Saiedi**, Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his gracious supervision, valuable guidance, generous help, support and continuous encouragement through the whole research. I am deeply affected by his noble character, perfection, care and consideration. I am very much privileged and honored to have him as my supervisor. To him I owe much more than I can express.

I would like also to express my most sincere thanks and deepest gratitude to **Dr. Salwa Omar El-Khattab**, Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for her remarkable effort, valuable comments and sincere advices.

Special thanks for **Dr. Hany Ahmed Abd El-Kader**, Lecturer of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, without whom this work couldn't have been completed. He gave me more time and more help to gather the information, reading and correcting it with great care.

Finally no words can express the warmth of my feeling to my family for their patience and help.

Beshoy Nabil Maoud
Cairo, 2013

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List of Abbreviations

Ach : Acetylcholine
Ach E : Acetylcholine esterase
AED : Anti-epileptic drug
AMPA : α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BAEPs : Brainstem auditory evoked potentials
BBB : Blood brain barrier
BIPLEDs : Bilateral independent Periodic lateralized epileptiform discharges
CBF : Cerebral blood flow
CMR : Cerebral metabolic rate
$CMRO_2$: Cerebral metabolic rate of oxygen
CNS : Central nervous system
CPP : Cerebral perfusion pressure
CSE : Convulsive status epilepticus
CSF : Cerebrospinal fluid
CT : Computerized topography
CVP : Central venous pressure
CVR : Cerebrovascular resistance
ECG : Electrocardiogram
ECoG : Electrocorticography
EEG : Electroencephalogram
EMG : Electromyogram
$ETCO_2$: End tidal CO_2
EVs : Evoked potentials
GABA : Gamma amino butyric acid
GCSE : Generalized convulsive status epilepticus

GPEDs : Generalized periodic epileptiform discharges
IBP : Invasive blood pressure
ICP : Intracranial pressure
ICU : Intensive care unit
IEDs : Interictal epileptiform discharges
IM : Intra muscular
IOM : Intraoperative neurophysiologic monitoring
IV : Intra venous
IVH : Intra ventricular hemorrhage
MAC : Minimal alveolar concentration
MAP : Mean arterial pressure
MEPs : Motor evoked potentials
MRI : Magnetic resonance imaging
NCSE : Non convulsive status epilepticus
NIBP : Noninvasive blood pressure
NMBs : Neuromuscular blockers
NMDA : N-methyl-D-aspartate
P_aCO2 : Arterial carbon dioxide partial pressure
P_aO2 : Arterial oxygen partial pressure
PCV : Packed cell volume
PET : Positron emission tomography
PLEDs : Periodic lateralized epileptiform discharges
rCVR : regional cerebrovascular resistance
RSE : Refractory status epilepticus
SE : Status epilepticus
SEPs : Somatosensory evoked potentials
SLE : Systemic lupus erythematous
SPECT : Single photon emission computed tomography
TcMEP : Transcranial electrical motor potential
TIVA : Total intra venous anesthesia
VAE : Venous air embolism

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Neurophysiological and neuroanatomical introduction and differences between adults and children

Neurotransmission

Synaptic transmission is the process by which signaling molecules called neurotransmitters are released by a neuron (the presynaptic neuron), and bind to and activate the receptors of another neuron (the postsynaptic neuron). Neurotransmission usually takes place at a synapse, and occurs when an action potential is initiated in the presynaptic neuron. The binding of neurotransmitters to receptors in the postsynaptic neuron can trigger either short term changes, like changes in the membrane potential called postsynaptic potentials, or longer term changes by the activation of signaling cascades **(Dilip& Cynthia, 2011).**

Stages in neurotransmission at the synapse are: Synthesis of the neurotransmitter. This can take place in the cell body, in the axon, or in the axon terminal. Then Storage of the neurotransmitter took place in storage granules or vesicles in the axon terminal. Followed by Calcium enters the axon terminal during an action potential, causing release of the neurotransmitter into the synaptic cleft which binds to and activates a receptor in the postsynaptic membrane (Fig.1). Then deactivation of the neurotransmitter. The neurotransmitter is either destroyed enzymatically, or taken back into the terminal from which it came, where it can be reused, or degraded and removed **(Geoffrey, 2007).**

Summation

Each neuron connects with numerous other neurons, receiving numerous impulses from them. Summation is the adding together of these impulses at the axon hillock. If the neuron only gets excitatory impulses, it will also generate an action potential. If instead the neuron gets as many inhibitory as excitatory impulses, the inhibition cancels out the excitation and the nerve impulse will stop there. Spatial summation means that the effects of impulses received at different places on the neuron add up, so that the neuron may fire when such impulses are received simultaneously, even if each impulse on its own would not be sufficient to cause firing. Temporal summation means that the effects of impulses received at the same place can add up if the impulses are received in close temporal succession. Thus the neuron may fire when multiple impulses are received, even if each impulse on its own would not be sufficient to cause firing **(Yadav et al., 2008).**

Convergence and divergence

Neurotransmission implies both a convergence and a divergence of information. First one neuron is influenced by many others, resulting in a convergence of input. When the neuron fires, the signal is sent to many other neurons, resulting in a divergence of output. Many other neurons are influenced by this neuron **(Dilip& Cynthia, 2011).**

Co-transmission

Co-transmission is the release of several types of neurotransmitters from a single nerve terminal. Recent studies in a myriad of systems have shown that most, if not all; neurons release several different chemical messengers. Co-transmission allows for more complex effects at postsynaptic receptors, and thus allows for more complex

communication to occur between neurons. In modern neuroscience, neurons are often classified by their co-transmitter. For example, striatal "GABAergic neurons" utilize opioid peptides or substance P as their primary co-transmitter. Some neurons can release at least two neurotransmitters at the same time, the other being a co-transmitter, in order to provide the stabilizing negative feedback required for meaningful encoding, in the absence of inhibitory interneurons. Examples include: GABA–glycine co-release and Dopamine–glutamate co-release **(Trudeau & Gutiérrez, 2007).**

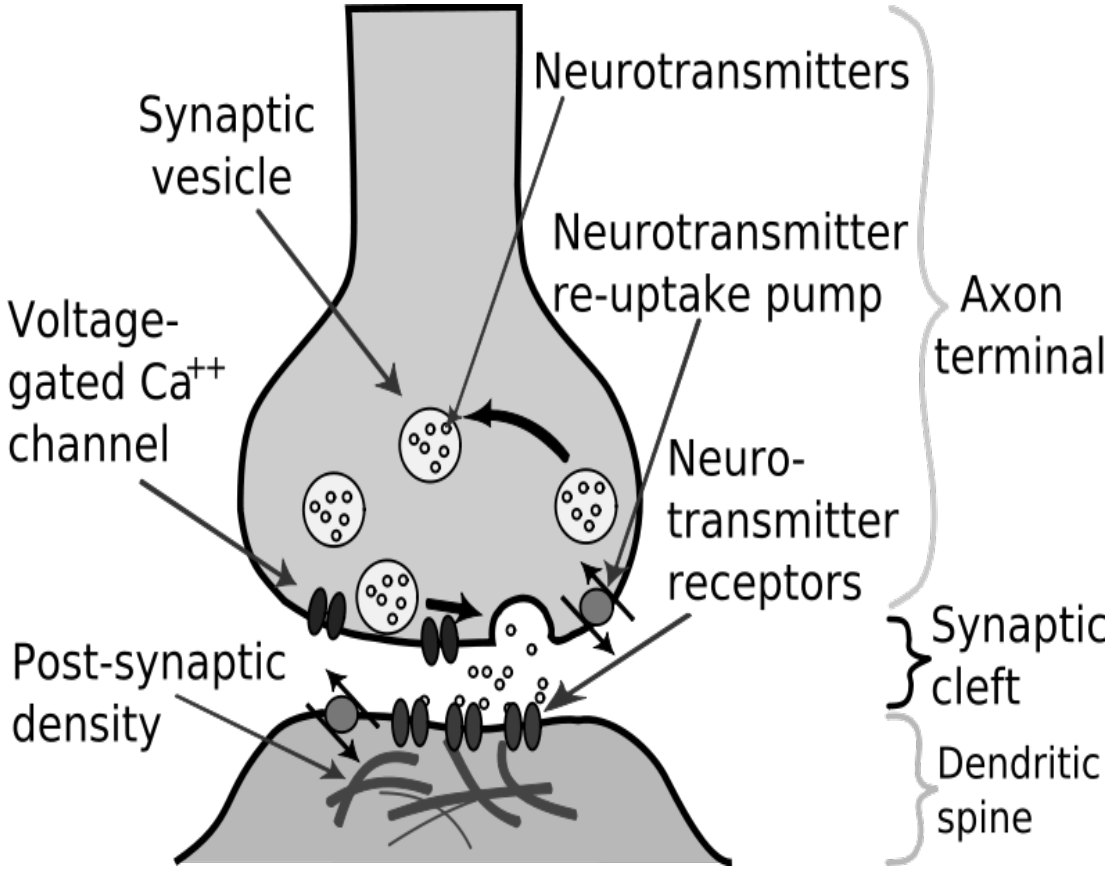

Figure-1 Synaptictransmission **(Dilip& Cynthia, 2011).**

Neurotransmitters

Neurotransmitters are endogenous chemicals that transmit signals from a neuron to a target cell across a synapse. Neurotransmitters are packaged into synaptic vesicles clustered beneath the membrane in the axon terminal, on the presynaptic side of a synapse. They are released into

and diffuse across the synaptic cleft, where they bind to specific receptors in the membrane on the postsynaptic side of the synapse. Release of neurotransmitters usually follows arrival of an action potential at the synapse, but may also follow graded electrical potentials. Low level "baseline" release also occurs without electrical stimulation. Neurotransmitters are synthesized from plentiful and simple precursors, such as amino acids, which are readily available from the diet and which require only a small number of biosynthetic steps to convert **(Robert Sapolsky, 2005).**

Types of neurotransmitters and their actions

Some neurotransmitters are commonly described as "excitatory" or "inhibitory". The only direct effect of a neurotransmitter is to activate one or more types of receptors. The effect on the postsynaptic cell depends, therefore, entirely on the properties of those receptors. It happens that for some neurotransmitters (for example, glutamate), the most important receptors all have excitatory effects: that is, they increase the probability that the target cell will fire an action potential. For other neurotransmitters, such as GABA, the most important receptors all have inhibitory effects (although there is evidence that GABA is excitatory during early brain development). There are, however, other neurotransmitters, such as acetylcholine, for which both excitatory and inhibitory receptors exist; and there are some types of receptors that activate complex metabolic pathways in the postsynaptic cell to produce effects that cannot appropriately be called either excitatory or inhibitory. Thus, it is an oversimplification to call a neurotransmitter excitatory or inhibitory nevertheless it is convenient to call glutamate excitatory and GABA inhibitory so this usage is seen frequently **(Jonathan et al., 2013).**

A neurotransmitter must be broken down once it reaches the post-synaptic cell to prevent further excitatory or inhibitory signal transduction. For example, acetylcholine (ACh), an excitatory neurotransmitter, is broken down by acetyl-cholinesterase (AchE) **(Kodirov et al., 2006).**

Choline is taken up and recycled by the pre-synaptic neuron to synthesize more ACh. Other neurotransmitters such asdopamine are able to diffuse away from their targeted synaptic junctions and are eliminated from the body via the kidneys, or destroyed in the liver. Each neurotransmitter has very specific degradation pathways at regulatory points, which may be the target of the body's own regulatory system or recreational drugs **(Kodirov et al., 2006).**

Physiology of cerebral blood flow (CBF)

Blood brain barrier (BBB)

The blood–brain barrier is composed of high-density cells restricting passage of substances from the bloodstream much more than endothelial cells in capillaries elsewhere in the body. Capillaries in the brain (and spinal cord) are characterized by lack of fenestrations and abundant light junctions (zounlaeoccludens) between endothelial cells (Fig.2). This is the principal structural reason for the blood brain barrier which operates to protect the internal environment of neural tissue by allowing only selected substances (amino acids, amines and sugars) to be transported across the endothelial cells. This protective mechanism is possibly assisted by a basal lamina that is thicker than usual and by enveloping foot processes of astrocytes. Among the more important parts of the brain that have no blood brain barrier are the posterior pituitary, pineal body, median eminence of the hypothalamus **(Cottrell & Young, 2010).**

BBB is an effective, although not complete, barrier to charged particles (e.g., electrolytes), polar compounds (e.g., glucose, mannitol, amino acids), and larger molecules (e.g., proteins). Substances that are unimpeded by the BBB include water, lipid-soluble compounds (e.g., volatile anesthetics), and gases (e.g., oxygen, carbon dioxide, nitrous oxide). Access to the brain interstitium can be obtained by these particles and compounds through facilitated diffusion (glucose), active transport (ions), or pinocytosis (proteins) **(Liu et al., 2012).**

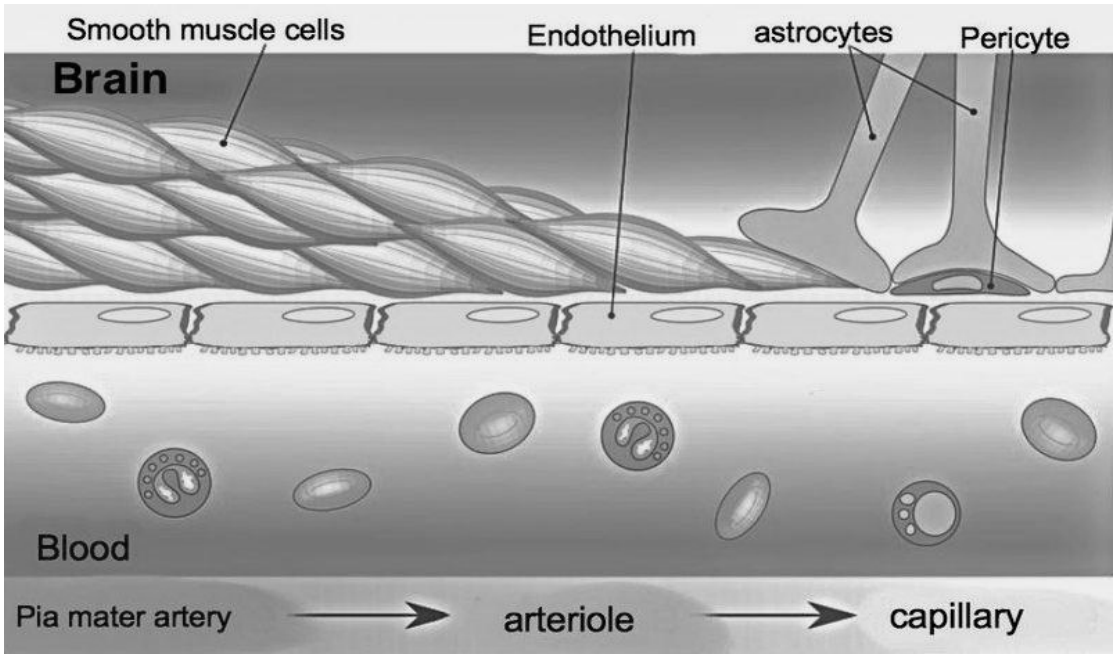

Figure-2 The Blood brain barrier **(Hamilton et al., 2007).**

Epilepsy is a neurological disease which characterized by recurrent and sometimes untreatable seizures. Several clinical and experimental data have implicated the failure of blood–brain barrier function in triggering chronic or acute seizures. Some studies implicate the interactions between a common blood protein (albumin) and astrocytes. These findings suggest that acute seizures are a predictable consequence of disruption of the BBB by either artificial or inflammatory mechanisms. In addition, expression of drug resistance molecules and

transporters at the BBB are a significant mechanism of resistance to commonly used anti-epileptic drugs **(Oby et al., 2006)**.

Prior to 2010, scientists believed that the blood-brain barrier did not develop until after birth, based on the belief that astrocytes did not develop until after birth. Researchers at Stanford University and the University of California, San Francisco, discovered in 2010 that pericytes which also required for blood-brain barrier development and that pericytes are present in the fetal brain. The research proves that your infant's blood-brain barrier is fully developed well before birth **(Tortora et al., 2010).**

Cerebral metabolic rate (CMR)

The cerebral metabolic rate (CMR) of oxygen ($CMRO_2$) is defined as the amount of oxygen consumed by the brain in normal state. The brain and the heart are at highest risk for ischemia due to their high oxygen utilization and relatively low physiologic reserve **(Morgan et al., 2006).**

With respect to the brain, this susceptibility stems from its high metabolic demand and its lack of significant anaerobic metabolism to support function in times of decreased oxygen or glucose substrate. Interruption of cerebral perfusion usually results in unconsciousness within 10 seconds as oxygen tension rapidly drops below 30 mm Hg. The window of time for development of severe irreversible brain damage from hypoxemia is approximately 3 to 8 minutes at normal body temperature. Brain glucose consumption is approximately 5 mg/100 g/min, of which over 90% is metabolized aerobically. $CMRO_2$ therefore normally parallels glucose consumption. Acute sustained hypoglycemia is equally as devastating as hypoxia. Paradoxically, hyperglycemia can exacerbate global and focal hypoxic brain injury by accelerating cerebral acidosis and cellular injury. In