Neurodevelopmental Effects of General Anesthesia in Neonates

Essay
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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ

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List of Abbreviations

Ach	:	Acetylcholine
ADNP	:	Activity-Dependent Neuroprotective Protein
AIDN	:	Anesthetic induced developmental neurotoxicity
Akt	:	Adams Kara Taylor
ATP	:	Adenosine-5'-triphosphate
Aβ	:	Beta-amyloid
BAPTA	:	1,2-bis(o-aminophenoxy)ethane-tetraacetic acid
Bax	:	Bcl-2–associated X protein
BDNF	:	Brain derived neurotrophic factor
C	:	Complement compound
Ca^{2+}	:	Calcium
CaBPs	:	Calcium binding proteins
CaMKII	:	Calmodulin-dependent protein kinase
CNS	:	Central nervous system.
EAAs	:	Excitatory amino acids
EEG	:	Electroencephalogram
EPO	:	Erythropoietin
EpoR	:	Epo receptor
ER	:	Endoplasmic reticulum
GABA	:	Gamma-amino butyric acid
GAP-43	:	Growth associated protein-43
GSK-3β	:	Glycogen synthase kinase 3
HIF-1α	:	Hypoxia-inducible factor 1-alpha protein
IL	:	Interleukin
IP3	:	Inositiol triphosphate
IV	:	Intravenous
KCC	:	K^+/Cl^- cotransporter
LTP	:	Long-term potential
MAC	:	Minimal alveolar concentration

List of Abbreviations (Cont.)

mBDNF	:	Mature Brain-derived neurotrophic factor.
MDI	:	Mental development index
MFG	:	Middle frontal gyrus
MLC	:	Myosin light chain protein
mPTP	:	Mitochondrial permeability transition pore
mRNA	:	Messenger Ribonucleic acid
NGF	:	Nerve growth factor
NMDA	:	N-methyl-D- aspartate
NR1	:	NMDA Receptor subunit 1
NT-3	:	Neurotrophin-3
P75NTR	:	P75 neurotrophin receptor
PARP	:	Poly-(ADP-ribose) polymerase
pERK	:	Extracellular-signal-regulated kinase
PET	:	Positron emission tomography
PFC	:	Prefrontal cortex
pJNK	:	Phospho-Jun N-terminal kinase
PKCα	:	Protein Kinase Cα
PNDs	:	Post natal days
PPX	:	Pramipexole
rEPO	:	Recombinant Epo
RhoA	:	Ras homolog gene family, member A
ROS	:	Reactive oxygen species
TBV	:	Total brain volume
TNF-α	:	Tumor necrosis factor
tPA	:	Tissue plasminogen activator
Trk	:	Tyrosine kinase
VDCCs	:	Voltage-dependent calcium channels

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Introduction

Studies suggest that prolonged exposure to general anesthetics may induce widespread neuronal cell death and neurological sequelae; seriously questioning the safety of pediatric anesthesia. There is mounting and convincing preclinical evidence in rodents that anesthetics in common clinical use are neurotoxic to the developing brain in vitro and cause longterm neurobehavioral abnormalities in vivo. Several human cohort studies had demonstrated an association between major surgery in the neonatal period and poor neurodevelopmental outcome. The risk of learning disability increased with the number of anesthetics the child had received. Interestingly, there was no evidence for an increased risk of association after just one exposure **(Reddy, 2012)**.

Development is characterized by 2 major organizational periods. The first period begins at conception and includes the major histogenetic events such as neurulation, proliferation, migration, and differentiation. It has been proposed that these events may be controlled by genetic events, which give rise to neural structures that are amenable to external influence. The second period is a time of reorganization in the human cortex. These events occur

during gestation and continue postnatally, possibly through the 2nd decade of life. This stage is characterized by dendritic and axonal growth, synapse production, neuronal and synaptic pruning, and changes in neurotransmitter sensitivity. Although the initiation of these events is influenced by endogenous signals, further neural maturation is primarily influenced by exogenous signals **(Webb et al., 2001).**

The mechanism of anesthetic-induced enhancement of neuroapoptosis and neurodevelopmental impairment is not clear. The diverse group of clinically used general anesthetics spans from intravenous IV anesthetics such as benzodiazepines, barbiturates, ketamine, propofol, and etomidate, to inhaled anesthetics, such as halothane, isoflurane, sevoflurane, desflurane, nitrous oxide, and xenon. Although these compounds are chemically very dissimilar, strikingly, their proposed mechanisms of action that inhibit neuronal activity is very similar, entailing, to varying degrees, alterations of synaptic transmission involving gamma-amino butyric acid (GABA) and/or N-methyl-D- aspartate (NMDA) receptors**.** Because GABA and NMDA-mediated neuronal activity is essential for mammalian brain development, exposure to general

anesthetics could potentially interfere with normal brain maturation **(Campagna et al., 2004).**

Some neuroprotectants are reported to alleviate anesthetic-induced neurotoxicity in the developing brain such as Erythropoietin, Nicotinamide, Vitamin D3, Vitamin C, Alpha2 (α_2) Adrenoceptor Agonist, Lithium and Melatonin **(Lei et al., 2012).**

Aim of The Work

The aim of this work is to review the current literature as regard the effects of exposure to general anesthesia in neonates and infants on the development of their nervous system, possible longterm neurodevelopmental sequelae and possible implications for pediatric anesthesiologists.

Chapter 1

Early development of the human nervous system and neurocognitive function

Early in development, there is initially an overproduction and redundancy in synaptic connections. But with maturation, increases in sensory input from the environment further influence neural patterning. The circuits that persist may be the circuits that benefit from the greatest amount of activity, but those that remain unspecified regress. This initial redundancy in synaptic connections, followed by their elimination, may be universal to all neuronal systems **(Webb et al., 2001).**

The initial overproduction in the cortex may be related to the functional property of the immature brain to allow recovery and adaptation after focal injury or malformation and may represent a critical or vulnerable period **(Huttenlocher, 1984).**

This overproduction may also be the mechanism by which the brain is made ready to receive specific input from the environment. Studies of synaptogenesis demonstrate important developmental increases in the postnatal period. The period of early overgrowth is important for the onset of cognitive function **(Goldman and Rakic, 1987).**

Stages of neurobiological development include: Axonal and dendritic development, Synaptogenesis and stabilization of synaptic functions (Neurotransmission) and Myelination **(Webb et al., 2001).**

Axonal and Dendritic Development:

Axons are the primary mechanism by which neurons signal other neurons in the cortex and often must travel over several centimeters to reach their targets. The neuron sends out an axon to its synaptic target. Most axons travel along simple linear pathways **(Jessell, 1988)**.

Unfortunately, the formation of appropriate axonal projections may be disrupted in a number of ways. Early postnatal head trauma may block the pathway of axons due to tissue scarring. Anoxia, toxins, malnutrition, or genetic anomalies may alter path formation **(Li et al., 1994).**

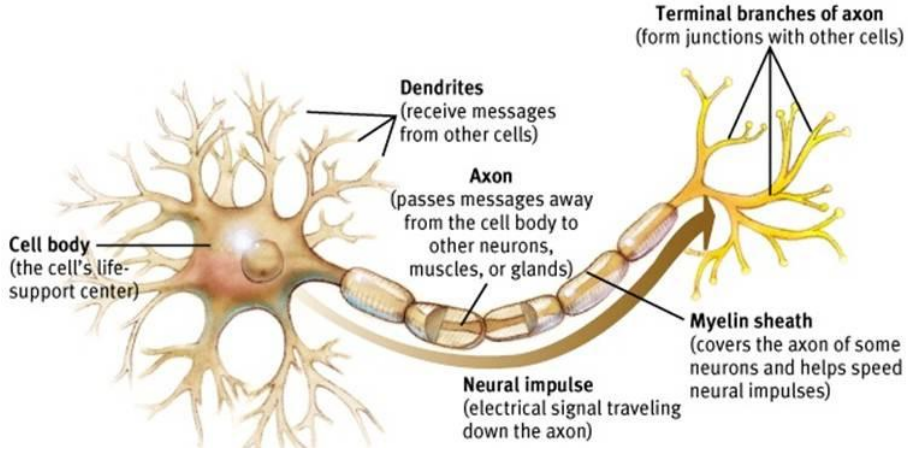

Figure 1. The neuronal cell **(Enchanted learning, 2009).**

There seems to be two mechanisms driving the early outgrowth of pyramidal neuron dendrites. First, due to genetically determined, activity-independent signals, neurons form early dendritic processes soon. As cells develop receptor mechanism at their neuronal bodies, spontaneous electrical activity may signal the initial development of dendrites. Second, incoming axon processes can induce dendrites to form **(Webb et al., 2001).**

Further dendritic differentiation and elaboration may be dependent on the establishment of afferent input. Thus, receiving early connections is of critical importance for organization. Course of dendritic sprouting, which begins to form as soon as approximately 15 weeks with spines typically appearing on both pyramidal and non-pyramidal neurons between the 25th to the 27th weeks of gestation and increasing through the 24^{th} postnatal month in some cortical regions **(Mrzljak et al., 1990).**

Dendrites first appear as thick processes extending from the cell body with only a few spines. These first dendrites are both apical (extending from the peak of the neuron and crossing several layers toward the surface) and basilar (extending parallel to the surface within the same layer). As dendrites thicken and increase in number, they