New Insights Into Anesthetic Mechanisms

Essay

Submitted by

Andrew Yousry Louis
M.B., B.Ch.
Faculty of Medicine
Ain Shams University

For the partial fulfillment of Master Degree in Anesthesiology

Supervised by

Prof. Dr. Azza Abd Elrashid Hassan
Professor of Anesthesiology
Faculty of Medicine
Ain Shams University

Dr. Ahmed Mohamed Shafik Hamed
Assistant professor of Anesthesiology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2013

Acknowledgment

My deepest gratitude and thanks to **Allah** the most merciful for guiding me through and giving me the strength to complete this work.

I would like to express my deepest thanks and profound respect to my honored **Prof. Dr. Azza Abd Elrashid Hassan**, Professor of Anesthesiology for her kind encouragement, guidance, support, and patience she gave me throughout the whole work. It has been an honor and privilege to work under her generous supervision.

I found no words by which I can express my deepest thanks and appreciation to **Dr. Ahmed Mohamed Shafik Hamed**, Assistant professor of Anesthesiology for his great support, valuable time, and continuous advices which helped me to overcome many difficulties.

I finally owe my great thanks and appreciation to **My Parents** who supportted me greatly until this work come to light.

Contents

List Of Tables

List of Figures

List of abbreviations

µM	Micro Mole
2PK	Two-pore domain potassium channels
4CmC	4-chloro-m-cresol
5HT3	5-hydroxy tryptamine receptors type 3
Å	Ångstrom
ABD	Agonist-Binding Domain
AD	Autosomal Dominant
ADNP	Activity-Dependent Neuroprotective Protein
ADP	Adenosine diphosphate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid
AP	Action potential
AR	Autosomal Recessive
AT_{1A}	Angiotensin AT_{1A} receptor
ATD	Extracellular Amino-Terminal Domain
Atm	Atmospheric
ATP	Adenosine Triphosphate
BDNF	Brain-derived neurotrophic factor
BF	Basal Forebrain
BFNC	Benign familial neonatal epilepsy
Ca^{2+}	Calcium

List of abbreviations

cAMP	Cyclic adenosine monophosphate
cDNA	Complementary DNA
CF	Cystic fibrosis
Chl	Chloroform
CK	Creatine Kinase
Cl^-	Chloride
CNS	Central Nervous System
CO_2	Carbon Dioxide
CP	Creatine Phosphate
DAG	Diacylglycerol
DEKA	Amino acid sequence (Asp-Glu-Lys-Ala)
Des	Desflurane
DM	Dystrophic myopathy
DMPC	Dimyristoylphosphatidylcholine
DNA	Deoxyribonucleic acid
DRG	Dorsal root ganglia
E.N.T.	Ear, Nose, and Throat
EC	Extracellular (domain)
EC_{50}	Half maximal effective concentration
E_K	Nernst potential for potassium

List of abbreviations

E_{Na}	Nernst potential for sodium
Enfl	Enflurane
Epo	Erythropoietin
E_{rev}	Nernest reversal potential
Eth	Ethanol
Ether	Diethyl ether
Etom	Etomidate
$GABA_A$	Gamma amino butyric acid receptor type A
GAs	General Anesthetics
GDP	Guanosine diphosphate
GPCRs	G-protein-coupled receptors
GSK	Glycogen synthase kinase
GTP	Guanosine triphosphate
H_2	Histamine type 2 receptor
Hal	Halothane
HCN3	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 3
IC	Intracellular (domain)
IC_{50}	Median Inhibitory Concentration
IFM	Amino acid sequence (isoleucine–phenylalanine–methionine)

List of abbreviations

IL	Interleukins
IP3	Inositol triphosphate
Isofl	Isoflurane
IVCTs	In vitro contraction tests
K^+	Kalium (Potassium)
KI	Potassium iodide
LC	Locus coeruleus
LDT	Laterodorsal tegmental nuclei
M_{1-3}	Muscarinic M_{1-3} receptor
mEq	Milliequivalent
Mexyfl	Methoxyflurane
MH	Malignant Hyperthermia
mM	milliMole
MOC	Methoxycarbonyl
MR spectroscopy	Magnetic resonance spectroscopy
ms	Millisecond
mV	Millivolt
N_2O	Nitrous oxide
Na^+	Natrium (sodium)
nACh	Nicotinic acetylcholine

List of abbreviations

nAChR	Nicotinic acetylcholine receptor
nM	Nanomole
NMDA	N-methyl-D-aspartate
Pa	Pascal
pA	Pico Ampere
$PaCO_2$	Partial Pressure of Carbon Dioxide in Arterial Blood
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PDB	Protein Data Bank
pH	Potential of Hydrogen - negative 10-base log (power) of the positive hydrogen ion concentration; measure of acidity
PHHI	Persistent hyperinsulinemic hypoglycemia of infancy
PI	Phosphate (Inorganic)
PND	Postnatal day
pKa	Negative log of ka (acid dissociation constant)
POCD	Postoperative cognitive dysfunction
PONV	Postoperative nausea and vomiting
Ppb	Pentobarbital
PPT	Pedunculopontine tegmental nuclei
Pro	Propofol

List of abbreviations

psi	Pound per square inch
QX 314	Quaternary derivative of lidocaine
ROS	Reactive oxygen species
Sevo	Sevoflurane
SH	Src homology
SpO_2	Saturation of Peripheral Oxygen
SR	Sarcoplasmic reticulum
SV	Spontaneous ventilation
TM	Transmembrane (domain)
TM2	Second transmembrane domain
TMN	Tuberomammillary nucleus
TNF	Tumor necrosis factor α
T-tubule	Tranverse tubule
TTX	Tetrodotoxin
VLPO	ventrolateral pre-optic nucleus
WHO	World Health Organization

Introduction

Over time humankind has employed an array of natural medicines and physical methods to alleviate pain and suffering. Ancient Indian and Chinese texts record the beneficial analgesic effects of cannabis and henbane. In Egypt around 3000 B.C., the opium poppy, hellebore, beer, and the legendary mandrake were used for similar purposes. Other approaches to deal with surgical trauma and pain relied on physical methods such as cold, nerve compression, carotid artery occlusion, or infliction of a cerebral concussion. The effectiveness of these historical agents is unknown but alludes to an ever present need ***(Brandt, 1997)***.

A new era of anesthesia arose as one of the advancements of the Enlightenment. It began with the isolation of oxygen and the synthesis of nitrous oxide in the 1770's by Joseph Priestley. Initially, nitrous oxide was used solely as an intoxicant. American dentist, Horace Wells was the first to recognize the anesthetizing potential of nitrous oxide; however, his attempt to produce surgical anesthesia in 1845 with this weak anesthetic was a miserable failure ***(Brandt, 1997)***.

Another compound, known as 'sweet vitriol' by Paracelsus and renamed ether in 1730 by German chemist Frobenius, proved to be more potent. It was used for the first successful public demonstration of surgical anesthesia, conducted by William Thomas Green Morton in Boston in 1846, the year after Wells'

failure. Prior to this, Crawford Long, an American physician practicing in Georgia had performed surgery under ether anesthesia as early as 1842. In 1847, Scottish physician Sir James Young Simpson succeeded in demonstrating anesthesia with chloroform, which had been discovered in 1831 by Souberain, Guthrie and Liebig. Chloroform was used by John Snow to oversee the painless delivery of Queen Victoria's eighth child, Leopold, in 1850 ***(Brandt, 1997).***

Fast forward to today, a large number of drugs are available to the modern anesthetist to produce general anesthesia, from intravenously administered hypnotics to halogenated vapors and gaseous agents such as xenon. The intravenous hypnotics, which provide a smooth induction of anesthesia, include barbiturates such as sodium pentothal, introduced in 1934 in America by Lundy; etomidate, introduced and studied by Doenicke in 1973, and propofol, which has been widely accepted since its introduction in 1977. The structures of these disparate agents and others are shown in Fig. 7. This dissertation will take a broad look at the mechanisms of action of both general and local anesthetics and attempt to discriminate where they may overlap and where they may diverge ***(Lugli et al., 2009)***.

Research efforts have pursued a reductionist path to approach the difficult problem of assigning the clinical effect of an anesthetic to action at a single biological site. This so-called 'unitary theory' has animated efforts to produce a single molecular definition of the site of anesthetic action. Subsequent research has revealed a multitude of targets and produced a more complex picture of how clinically relevant doses of anesthetics affect molecular targets throughout the central nervous system (CNS). Ironically, in recent years research groups have discovered that a few discrete sites within the CNS may indeed mediate the action of some general anesthetics ***(Lugli et al., 2009)***