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General Anesthesia: A Literature Review - Induction, Mechanism, Agents, and Effects

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General Anesthesia: A Literature Review - Induction, Mechanism, Agents, and Effects

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General Anesthesia
A Literature Review
Induction, Mechanism, Agents, and Effects

by
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in Partial Fulfillment for the Requirements for Graduation
with Honors in Nursing

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General Anesthesia

A Literature Review

Induction, Mechanism, Agents, and Effects

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General Anesthesia

A Literature Review

Induction, Mechanism, Agents, and Effects

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Consciousness and Unconsciousness

General anesthesia is an essential component of modern medicine. It's a drug-induced, reversible condition that includes specific behavioral and physiological traits — unconsciousness, amnesia, analgesia, and akinesia — with concomitant stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems (Brown, Lydic, & Schiff, 2010). In the United States, nearly 60,000 patients a day receive general anesthesia for surgery. However, a deep and detailed understanding of its mechanism is lacking. “The mechanism by which general anesthetics prevent consciousness remains unknown largely because the mechanism by which brain physiology produces consciousness is unexplained” (Hameroff, 2006, p.400). In addition, it was previously believed that general anesthetics are drugs without receptors, but significant progress in the understanding of their mechanisms of action at the molecular, cellular and neural levels have been made.

Defining unconsciousness and exploring its relationship to general anesthesia, sleep, and coma, gives us a better explanation of how these agents work and could also lead to the development of better drugs with fewer side effects.

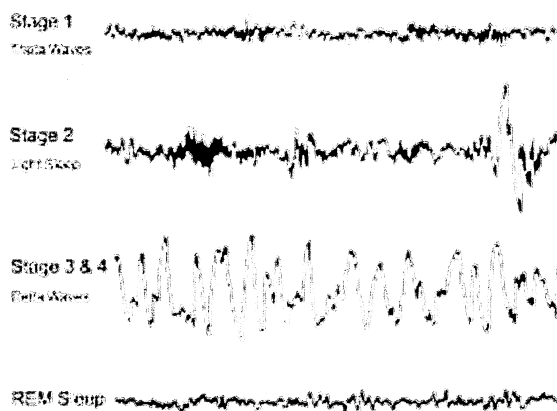
William James defined consciousness as the “awareness of oneself and the environment” (Hudetz, 2006, p.196). Awareness however, is none other than consciousness itself and the definition of the self is as elusive as that of consciousness. The essence of the self is the perceiving, thinking and willfully acting “I” that cannot exist without consciousness. Neurology goes further and separates consciousness into wakefulness and awareness. For

example, a patient in vegetative state has periodic wakefulness and awareness; a person can also be sleep-walking or sleep-eating. This demonstrates that a person can be using complex sensorimotor capacities with desynchronized EEG (thus being “awake”) but presumably in the absence of conscious pre-frontal control. This further illustrates that wakefulness and consciousness are different (Hudetz, 2006).

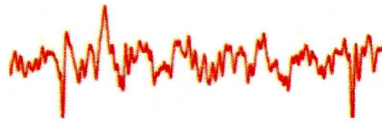
Sleep Cycles

Normal human sleep cycles between two states: rapid-eye-movement (REM) sleep and non-REM sleep, at approximately 90-minute intervals. REM sleep is manifested by rapid eye movements, dreaming, fluctuations in respiration and heart rate, penile and clitoral erection, and airway and skeletal-muscle hypotonia. In REM sleep, the EEG shows active high-frequency, low-amplitude rhythms. On the other hand, non-REM sleep has three distinct EEG stages, accompanied by higher-amplitude, lower-frequency rhythms with waning muscle tone, decreased body temperature, and decreased heart rate (Brown, Lydic, & Schiff, 2010).

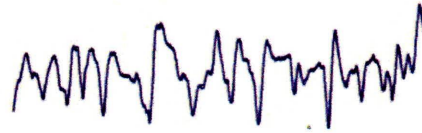
Sleep Stages



Light anesthesia



Deep anesthesia



In contrast, Brown, Lydic, & Schiff (2010) state that coma is a state of profound unresponsiveness, usually the result of a severe brain injury. Comatose patients cannot respond appropriately to vigorous stimulation. The patterns of EEG activity observed in comatose patients frequently resemble the high-amplitude, low-frequency activity seen in patients under general anesthesia. General anesthesia is, in fact, a reversible drug-induced coma.

Neural Correlate of Consciousness

The brain systems and their functional activities related to consciousness are known as the neural correlate of consciousness (NCC). According to Hameroff (2006), theoretically, consciousness can occur in corticocortical and thalamocortical networks, but can also arise in more localized and separate brain regions such as the brainstem and the limbic system. PET Scans and MRIs show that anesthetic induction and loss of consciousness correlate with reduced metabolic and blood flow activity in brainstem, thalamus, and various regions of cortex, including thalamocortical and corticocortical networks. However, these metabolic and hemodynamic decreases are secondary effects of loss of consciousness and not its cause.

In addition, an EEG analysis of anesthetic-induced loss of consciousness was conducted by John and Prichep and it was found that “loss of consciousness is a fairly abrupt transition of less than 20 ms involving interruption of synchrony between frontal and posterior cortical regions.” (Hameroff, 2006, p.401).

Cognitive Unbinding

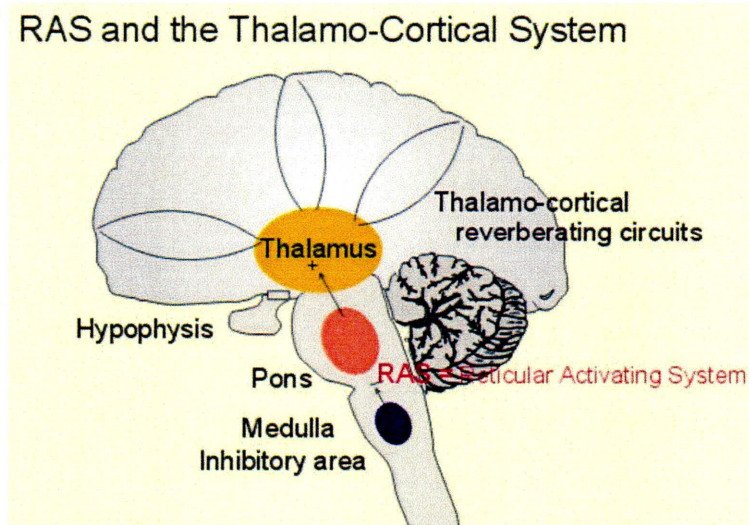
Mashour, Forman, & Campagna (2005) stated that anesthesia induces unconsciousness by the process of cognitive unbinding especially γ -synchrony previously mentioned. This leads to the question, what is cognitive binding? According to Mashour, Forman, & Campagna (2005), “cognitive binding occurs at virtually all levels of cognitive processing and is thought to be a crucial event for consciousness itself” (p. 358).

Three mechanisms are: binding by convergence, binding by assembly, and binding by synchrony. Binding by convergence is the process where lower-order neurons in more primary sensory areas converge upon secondary or higher-order areas for integration.

Cells have been identified that respond preferentially to particular objects, suggesting that they are attuned to synthesizing the perceptual data of an object into one representation.

Binding by assembly refers to an ensemble of cells in a neural circuit whose interconnections from distinct areas of the cortex allow the integration of different features of an object. Binding by synchrony is thought to be an important mechanism for cortical synthesis. Here, the correlation of neurons in time is thought to provide a flexible mechanism for integrating perceptual information processed in discrete areas of the brain. There is abundant evidence for temporal synchronization at different scales in the brain, associated with perceptual events and tasks. Binding by synchrony is due, in part, to

cortical resonance of 40 Hz with pacemaker neurons in the thalamus (Mashour, Forman, & Campagna, 2005). This, as Dr. Mashour (2014) proposed, proves that an interruption in any of these processes will lead to loss of consciousness. He added that, inhaled anesthetics were seen to interrupt the EEG signature 40-Hz coherence among rostral and caudal, as well as hemispheric brain regions, and that the γ -band synchronization that is typically observed between cortices in the conscious state was interrupted in the anesthetized state. Furthermore, according to Hameroff (2006), authorities state that only a small fraction of the brain's 100 billion or so neurons manifests the NCC at any one time, although many more are active which might explain why the anesthetized brain continues to respond to sensory stimuli.



A large region of the reticular formation of the brainstem is termed the ascending reticular activating system (RAS), which determines our state of consciousness, by its connection with the thalamocortical system.

According to Hudetz (2006), at an increasing dose, general anesthetic agents first produce amnesia, then sedation then unconsciousness, and finally, immobility and areflexia. The clinical signs and EEG patterns of this induced unconsciousness appear over three periods: induction, maintenance, and emergence. (Brown, Lydic, & Schiff, 2010).

Induction

The induction period begins with the administration of a hypnotic drug, a barbiturate, or an etomidate that act on GABA receptors and induce sedation with the patient being calm with the eyes closed, but is still arousable. The dose is then slowly increased, and here the patient may enter into a state of paradoxical excitation, manifested by purposeless or defensive movements, incoherent speech, euphoria or dysphoria. “This state is termed paradoxical because the drug that is intended to induce unconsciousness induces excitation instead.” (Brown, Lydic, & Schiff, 2010, p.2639). Here the Beta activity on EEG is increased to 13-25 Hz, while before induction, alpha activity was more prominent. When more of the hypnotic agent is administered, usually over a period of 10 to 15 seconds, an irregular respiratory pattern develops and progresses to apnea. This is where bag-mask ventilation is initiated to support breathing. Simultaneously, loss of response to oral commands and skeletal muscle tone occurs. Loss of consciousness can be easily assessed by having patients follow the movement of the anesthesiologist’s finger with their eyes. As unconsciousness takes place, eye tracking stops, blinking increases, corneal reflexes are lost, but the pupillary light reflex remains.

There can be either an increase or a decrease in blood pressure, but the heart rate typically increases. An opioid or a benzodiazepine before or during induction can be administered as well to decrease the effects on the heart rate, and a vasopressor can be given to maintain blood pressure. At the end of induction, a muscle relaxant is administered, along with tracheal intubation (Brown, Lydic, & Schiff, 2010).

Maintenance

A combination of hypnotics and inhalational agents, opioids, muscle relaxants, sedatives, and cardiovascular drugs, along with ventilatory and thermoregulatory support are used in the maintenance period. During this period, it is critical to monitor the adequacy of anesthesia and the patient's vital signs. If the level of anesthesia is inadequate, the heart rate and blood pressure can increase dramatically, along with perspiration, tearing, changes in pupil size, return of muscle tone, movement, and changes in EEG- all signs that alert the anesthesiologist to the possibility of increased nociception and arousal. According to Brown, Lydic, & Schiff (2010), there are four EEG patterns that define the phases of the maintenance period: Phase 1 is a light state of general anesthesia and decrease in EEG beta activity (13 to 30 Hz) and an increase in EEG alpha activity (8 to 12 Hz) and delta activity (0 to 4 Hz).²² In phase 2, beta activity decreases and alpha and delta activity increases. Phase 3 is a deeper state where the EEG is characterized by flat periods interspersed with periods of alpha and beta activity. The EEG in phase 2 and 3 are similar and resemble that on non REM sleep, and this is when surgery is usually performed. In phase 4, the most profound state of general anesthesia,

the EEG is isoelectric which can also be purposely induced by the administration of a barbiturate or propofol to protect the brain during neurosurgery or to stop generalized seizures. The amount of anesthesia drugs administered, their sites of action, pharmacokinetics, potency, and the patient's physiological status are all factors that affect the emergence from general anesthesia.

Emergence

During phase 1 of the emergence period, decreasing and stopping the anesthetic agents, and reversing neuromuscular blockers using reversal agents and brain stimulants take place. Additionally, regular breathing returns, and alpha and beta activity on EEG are increased. In phase 2, heart rate and blood pressure increase, autonomic responsiveness returns which includes responsiveness to painful stimulation, salivation, tearing, grimacing, swallowing, gagging, and coughing also return. Furthermore, return of muscle tone, defensive posturing, a further increase in alpha and beta activity on EEG, and extubation may occur in this stage. During phase 3, the patient will open his eyes and respond to some oral commands, and the EEG will show wakefulness patterns, and extubation definitely happens here if it didn't already take place in phase 2. The early clinical signs of emergence from general anesthesia such as the return of regular breathing, salivation, tearing, and swallowing, indicate return in brain stem function, while the late signs such as response to oral commands, indicate the return of cortical function. The patient should be able to answer simple questions and convey any discomfort, before he can be discharged from the PACU (Brown, Lydic, & Schiff, 2010).

<i>Stage</i>	<i>Respirations</i>	<i>Heart Rate</i>	<i>Blood Pressure</i>
Induction	Irregular/apnea	Increased	Decreased or increased
Maintenance	Steady/slow	Steady/slow	Normal
Emergence	Regular	Increased	Increased

Changes in Heart Rate, Respirations, and Blood Pressure
during Induction, Maintenance, and Emergence

According to Dr. Mashour (2014), balanced anesthesia is commonly used today. In the past, the patient was given a high dose of an inhaled anesthetic to achieve all the desired effects. Today, many drugs are given in low doses to achieve equilibrium and to avoid side effects: neuromuscular blockers, anticholinergics, sedatives-hypnotics, IV and inhaled anesthetics, opiates, paralytics can all be given. Forman & Chin (2008) state that general anesthetics can be classified into three groups based on their relative potencies for different clinical endpoints and their impact on EEG.

Group 1

Group 1 consists of the IV drugs etomidate, propofol, and barbiturates, which are much more potent at producing unconsciousness than immobilization, and are commonly used in the induction phase. According to Fox & Rowbotham (1999), propofol is the most studied drug, and since its introduction in 1984, no new intravenous anesthetic agents have been introduced. This drug leads to hypnosis at plasma concentrations around 3 µg/ml, whereas immobility during skin incision requires four-fold higher concentrations. These IV drugs shift cortical EEG toward lower frequencies by acting on a subset of γ -aminobutyric acid type A (GABAA) receptors. The GABAA receptors are neurotransmitter-gated chloride channels that are members of the ligand-gated ion channel superfamily that also contains nicotinic acetylcholine receptors, glycine receptors, and serotonin type 3 receptors. GABAA receptors are located both postsynaptically and extrasynaptically on neurons and when activated, they reduce neuronal excitation.

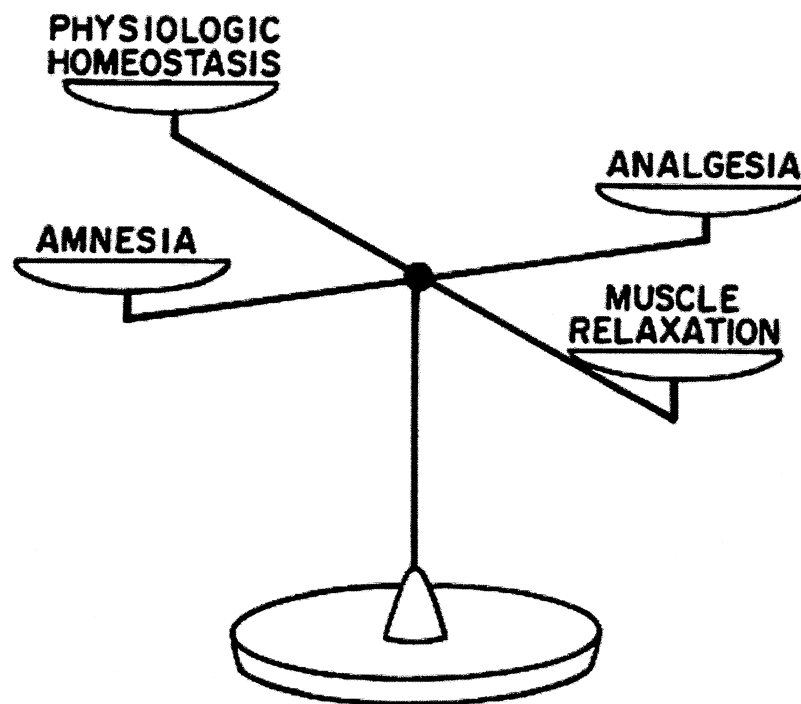
Furthermore, other studies have proposed that propofol-induced unconsciousness may be caused by indirect activation of cannabinoid receptors. It has been stated that propofol was found to inhibit fatty acidamide hydrolase, an enzyme that degrades the endogenous cannabinoid receptor agonist, anandamide. This mechanism may also contribute to the unusual anti-emetic properties of propofol (Forman & Chin, 2008).

Group 2

Group 2 includes the gaseous anesthetics nitrous oxide (N₂O), xenon (Xe) and cyclopropane, along with ketamine, an intravenous agent. In contrast to group 1 and group 3 drugs, these drugs produce significant analgesia while their potency as hypnotics and immobilizers is relatively weak. These drugs are usually used in the maintenance phase of anesthesia. Cardiovascular stability and a high frequency of reported dreamlike experiences are also features associated with Group 2 drugs. These drugs don't depress the EEG, but they actually increase cortical EEG frequencies, so EEG-based anesthetic depth monitoring is not reliable for detecting their effects. Unlike the drugs in group 1, the Group 2 drugs N₂O, Xe, cyclopropane, and ketamine have little to no effect on GABAA receptors. These drugs inhibit N-methyl-D-aspartate (NMDA) receptors which are excitatory cation channels activated by the amino acid glutamate. Glutamate receptors are the major excitatory neurotransmitter-gated ion channels in the brain, and are formed from a group of seven homologous subunits. In the presence of N₂O, Xe, cyclopropane or ketamine, NMDA receptor-mediated excitatory post-synaptic currents are markedly

inhibited, which leads to reduced excitatory signals in critical neuronal circuits, leading to unconsciousness (Forman & Chin, 2008).

Additionally, Forman & Chin (2008) stated that group 2 general anesthetics also affect members of the two-pore (2P) domain potassium channel family which regulates the resting membrane potential of neurons. Also, it has been stated that these drugs could also accomplish analgesia through their primary inhibitory action of NMDA receptors: excitatory amino acid transmission plays a role in nociception, which explains why antagonizing NMDA receptors results in analgesia as well (Duarte, McNeill, Drummond, & Tiplady, 2008).

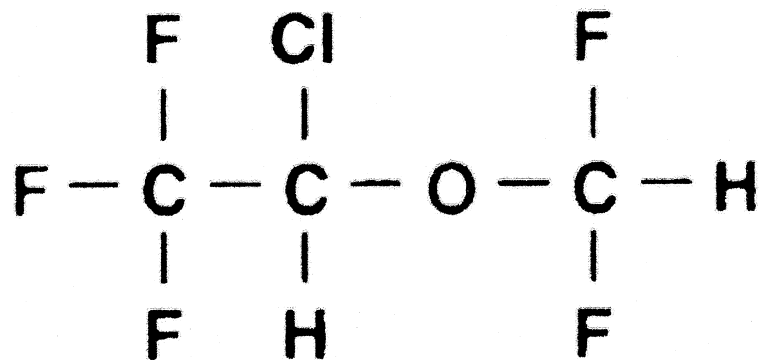


Balanced Anesthesia

Group 3

Group 3 drugs consist of halogenated ethers and alkanes volatile liquids anesthetics: halothane, enflurane, isoflurane, sevoflurane, and desflurane. These drugs induce amnesia, hypnosis and immobility, and reduce the frequency of cortical EEG. They produce amnesia at doses lower than those that produce unconsciousness (Forman & Chin, 2008). According to Dr. Mashour (2014), these drugs positively modulate GABAA receptors, but they have a more diverse molecular action on K⁺ channels and Ach receptors. However, pharmacologic and genetic studies suggest that volatile anesthetics produce unconsciousness via different GABAA receptor subunits than those targeted by the Group 1 drugs. Also, many two-pore domain K⁺ channels are activated by Group 3 general anesthetics which highly affect immobility rather than anesthesia. Similarly to N₂O, Xe and cyclopropane, the volatile anesthetics also inhibit NMDA receptors. In addition, a wide range of other ion channels are sensitive to Group 3 general anesthetics, including neuronal nicotinic ach receptors, serotonin type 3 receptors, Na⁺ channels, mitochondrial ATP-sensitive K⁺ channels, and cyclic nucleotide-gated HCN channels that mediate neuronal pacemaker currents (Forman & Chin, 2008). General anesthetics have traditionally been considered to be non-specific drugs. However, molecular pharmacology and transgenic animal studies are revealing that they are in fact quite selective for important CNS targets and structures that are critical for modulating the processes associated with consciousness. Overwhelming evidence points to the activity of the majority of anesthetics at ligand-gated ion channels,

providing an excellent rationale for their physiological effects. Enhancement of inhibitory function via GABA and/or glycine or background potassium channels, or inhibitions of excitatory pathways, such as NMDA are clearly providing hard targets and testable hypotheses. Understanding the mechanisms of action of these three groups have led to a better clinical application of general anesthetics; this explains why today, a combination of drugs is used in order to achieve different results, as opposed to just one drug.



Isoflurane

Due to all the advances in biological techniques, new avenues are being opened; and it's expected see a combination of these techniques along with transgenic technology to provide definitive answers to the role played by different ion channels in anesthesia, as well as the side effects of currently used drugs (Thompson & Wafford, 2001).

mechanisms of action as NMDA receptors antagonists. Neurotoxic effects were even more prominent when the exposure was to a combination of anesthetic agents with action on both NMDA and GABA receptors. This neurotoxicity was mostly the result of exposure that occurred at postnatal day 5 (Sun, 2010).

The Immature Brain

It appears that this neurotoxicity occurs in vulnerable brain regions of mammalian species especially during the peak of brain growth which is at the same time as synaptogenesis. This neuronal damage is apoptotic, resulting in massive DNA fragmentation; Both the intrinsic, or mitochondria-dependent apoptotic pathway and the extrinsic, death receptor-dependent pathway get activated by general anesthesia. In addition, general anesthesia was shown to cause disturbances in the homeostasis of the neurotrophic factors. Hence, the timing of anesthesia exposure during brain development is crucial in determining the severity of anesthesia-induced neurotoxicity, suggesting that the immature brain is most sensitive at the peak of its development (Jevtovic-Todorovic, 2010). Many behavioral studies of rats and mice indicate that exposure to general anesthesia at the peak of synaptogenesis does indeed cause learning and memory deficiencies, alters spontaneous behavior, and causes a lack of habituation later in life (Jevtovic-Todorovic, 2010). These findings raised concerns and lead the FDA to form a scientific advisory committee in 2007 to discuss if any changes in the use of anesthetic

agents in infants and children are needed, and more studies on humans started to emerge (Sun, 2010).

It has been thought that it is best to perform surgical procedures immediately after infants are born, before infants have bonded with family members, in order to prevent post-op psychological problems. However, this turned out to be the time of peak brain growth, when the brain is most vulnerable to anesthesia-induced neurotoxicity. This further supports the evidence that indicates the association of early exposure to anesthesia and neurocognitive deficits.

Learning Disabilities

Backman and Kopf(1986) were the first to report a possible relationship between anesthesia and long-term impairment of cognitive development. Based on a minor surgical procedure, the authors showed an increased incidence of cognitive impairments in children younger than 3 compared with preoperative baseline (Jevtovic-Todorovic, 2010).On the other hand, another population based, retrospective, birth cohort study that included 5357 children by Wilder et al.showed that a single exposure to general anesthesia was not associated with a greater risk of learning disabilities, children who received two or more general anesthetics were at a significantly increased risk that even further increased with longer cumulative duration of anesthesia exposure. Evidence shows that learning disability (maths,language, or reading) was higher in children with multiple anesthesia exposure and surgery before age 4.

Caesarean Delivery

A cohort of 5320 children was studied to specifically determine the neurocognitive effects of prenatal/fetal exposure during labor and delivery. The authors concluded that fetal exposure to general anesthesia during Caesarean delivery did not increase the risk for developing a learning disability compared with vaginal delivery without anesthesia (Sun, 2010). This retrospective study cohort, however, does not reflect the patient characteristics and cultural and racial and ethnic diversity of the overall US population. It also includes exposure to anesthesia from January 1976 to December 1982, a period where halothane and nitrous oxide were the most used anesthetics. Since the early 1980s, halothane and nitrous oxide use have declined.

Limitation of Retrospective Studies

Most studies were done retrospectively and could not control for the many variables that come into play during the perioperative period. They lack precise information in terms of age, agent, duration, and dose of anesthetics, specific agents used, the variable outcome endpoints used, and the way these outcomes were assessed, thus the findings might not be generalizable (Jevtovic-Todorovic, 2010).

Adjustment for Health Status

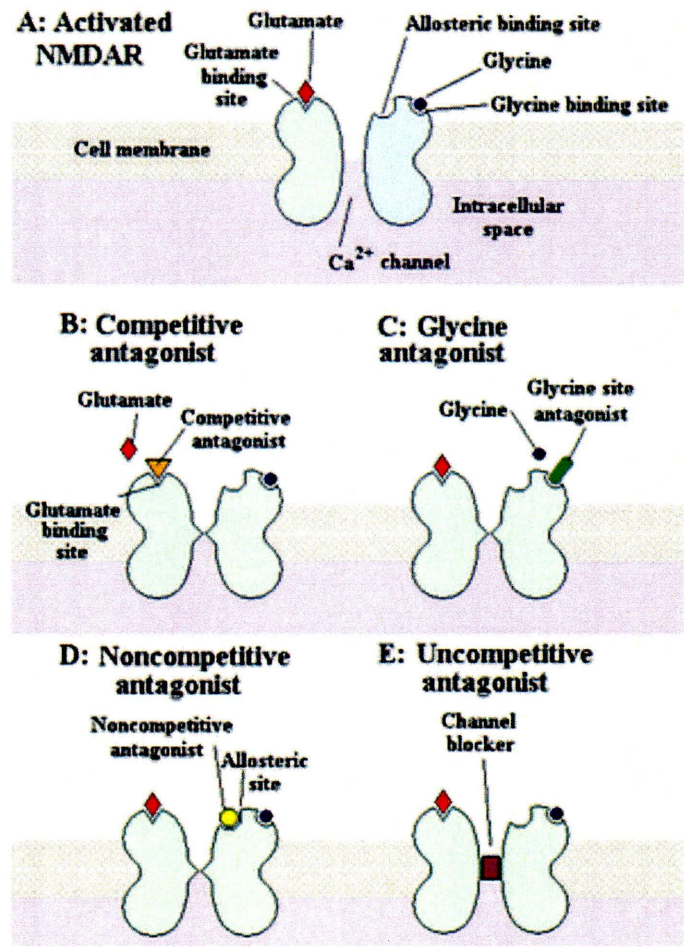
In a subsequent study, a population based birth cohort was used along with a matched cohort design that included adjustment for health status. Learning disabilities, receipt of an individualized education program (IEP) for disorders of emotion/behavior or speech-language, and group achievement tests were examined to determine if an

association exists between exposure to general anesthesia during the first 2 years of life and these outcomes (Flick et al., 2011). The cohort used includes 5357 children in the cohort, of whom, 350 underwent procedures that required general anesthesia before the age of 2, and the median duration of anesthetic exposure was 75 mins. Records for every child including results of all individually administered tests of intelligence and academic achievement, all group-administered tests of achievement and cognitive ability, as well as educational and socioeconomic information were included. The estimated cumulative incidence of learning disabilities at 19 years was 21.3% for unexposed controls, 23.6% for those exposed once, and 36.6% for those with multiple exposures. The main finding is that after adjustment for health status and matching for other factors associated with learning disabilities, exposure to anesthesia before the age of 2 was a risk factor for the development of learning disabilities and the need for an IEP for speech and language impairment in children with multiple, but not single, exposures (Flick et al., 2011).

ADHD

As mentioned before, NMDA receptor antagonists were the cause of extensive neuronal apoptosis in the developing rat brain. According to Sprung et al., (2012), this neural injury which is associated with hyperactivity that can be ameliorated by dextroamphetamine, has been proposed as a model for ADHD. Manifestations in children with ADHD include inattention, impulsivity, and motor restlessness, a clinical presentation consistent with a neuropsychological disorder. In addition to deficits in learning and memory in later behavioral studies. Frederickson et al al found that ketamine

given to neonatal rats and the rhesus monkey produced hyperactivity that could be ameliorated by dextroamphetamine, which is used to treat ADHD (Sprung et al., 2012). This study by Sprung et al., (2012), supports the results found in rodents and the rhesus monkey. It used a previously described cohort of 8548 children and examined the association between exposure to general anesthesia before age 2 years and ADHD. It concluded that multiple, but not single, exposures to procedures requiring general anesthesia during the first 2 years of life are associated with an increased incidence of ADHD.



	Deficit					
	Restricted Cohort			Full Cohort		
	Unexposed (%)	Exposed (%)	P Value	Unexposed (%)	Exposed (%)	P Value
CELf-T	5.4	14.3	0.0005	6.1	13.7	<0.0001
CELf-R	4.2	10.7	0.004	4.9	10.2	0.002
CELf-E	5.4	11.6	0.01	6.2	11.7	0.004
CPM	7.2	11.6	0.11	7.5	13.2	0.006
ICD9-B/L/C	27.5	41.1	0.004	23.6	41.6	<0.0001
ICD9-B	13.6	20.5	0.054	12.5	21	<0.0001
ICD9-L/C	20.9	35.7	0.0006	17.8	35.1	<0.0001
NWAMSE	9	13.4	0.14	9.5	12.7	0.25
RWAMSE	4.3	3.6	0.71	4.2	3.8	0.82
SWAMSE	11.4	14.3	0.37	11.5	13.7	0.46
WWAMSE	9.6	14.3	0.13	9.7	12.8	0.28

CELf = Clinical Evaluation of Language Fundamentals; CELf-E = CELf Expressive Language Score; CELf-R = CELf Receptive Language Score; CELf-T = CELf Total Score; CPM = Colored Progressive Matrices; ICD-9 = International Classification of Diseases, 9th Revision, Clinical Modification; ICD9-B/L/C = ICD-9-coded Behavioral, Language, and Cognitive Disorders; ICD9-B = ICD-9 coded Behavioral Disorders; ICD9-L/C = ICD-9 coded Language and Cognitive Disorders; NWAMSE = WAMSE Numeracy Test; RWAMSE = WAMSE Reading Test; SWAMSE = WAMSE Spelling Test; WAMSE = Western Australian Monitoring Standards in Education; WWAMSE = WAMSE Writing Test.

Association of Anesthesia Exposure before Age 3 yr and Deficit in Neuropsychological Test Scores, ICD-9-Coded Clinical Outcomes, and Academic Achievement Scores in the Restricted and Full Cohorts (Ing, et. al., 2012).

Ing and colleagues (2012) performed a study using a cohort of 2868 children, to examine the association between exposure to general anesthesia in children under age 3 and deficits present at age 10. In this study, directly administered neuropsychological assessments were used, including deficits found in language and abstract reasoning associated with anesthesia exposure. After birth, all children were assessed at 1, 2, 3, 5, 8, 10, 13, and 16 years of age. Parents were asked to keep detailed diaries of their child's medical history. During follow-up visits, parents filled out questionnaires describing illnesses and medical problems. There was no direct access to medical records after the perinatal period, including surgical and anesthetic records (Ing et. al., 2012). At each follow-up visit, neuropsychological testing was performed. The most extensive testing occurred at the 10-year follow-up visits where language, cognitive function, motor skills, and behavior were all tested.

When compared with unexposed children, evidence showed that children exposed to anesthesia had significantly worse scores in tests of receptive, expressive, and language. However, no differences were evident between exposed and unexposed children in behavior and motor function.

Autism

In a meta-analysis by Wang, Xu, & Miao (2014), the authors described a study by Hattori et al. who investigated the effect of anesthetic agents on the developmental disorders of children in an indirect way by investigating the children having undergone general anesthetic delivery. In a case series comparing 11,939 births in a hospital where anesthetic agents were administered during delivery, there were 0.2% cases of autistic disorder in the anesthetic-exposed group compared to 0.09% cases of autistic disorder in the unexposed group.

Other Factors to Consider

Wang, Xu, & Miao (2014) also found that exposure to anesthesia in children younger than 4 years is probably associated with later impairment in neurodevelopment. In addition, they stated that this positive association is influenced by the number of times of exposure to anesthesia but not timing of exposure, indicating that an early surgery in children is probably acceptable but doctors should try to avoid multiple times of anesthesia exposures. Furthermore, they state that early evidence also suggest that in a single procedure of surgery, the dose of anesthetic agents and time of anesthesia might have very limited influence on the neurodevelopmental outcomes. Wang, Xu, and Miao

(2014) state that pediatric anesthetic neurotoxicity is a complicated and complex issue, and there are many other variables to consider in addition to the potentially toxic effects of anesthesia. These include maternal health, drug exposures during pregnancy and delivery, preexisting medical conditions in the child, and environmental or ecological characteristics. Standard measurement forms should be used in neurocognitive assessments and different forms would result in different outcomes of neurodevelopmental assessment. This is why, given this complexity, observational studies are hard put to demonstrate unequivocal associations or risk. In addition, even though most studies show that the times of exposures and duration of anesthesia exposure are what is related to toxicity, it is important to remember that most studies are retrospective. Therefore, it is critical to have more research done and more studies that use directly administered neuropsychological assessments as outcome measures.

Surgery and Cancer

Surgery is usually the main treatment in the management of solid tumors because definitive resection can be totally curative. Therefore, it's critical to determine if anesthesia affects the prognosis of cancer, whether positively or negatively. Several studies have suggested that resection of cancers by surgeries using regional anesthesia could be associated with better outcomes as compared to those with general anesthesia in several types of cancer, including breast, colon, prostate, and ovary. In addition, early research has shown that general anesthetics might accelerate postoperative metastasis, and a recent study has suggested that volatile anesthetics could affect gene expression in human and brain tumor cell lines (Xie, 2013). Furthermore, Tavare et al. (2012) reported that Myles et. al published the first randomized controlled trial and examined the effect of epidural use on recurrence after a variety of major abdominal oncologic resections and found no change in duration of recurrence-free survival when compared to standard general anesthesia. However, numerous heterogeneous operations across a variety of distinct abdominal malignancies were analyzed together, and thus, an effect confined to specific cancers would be masked. The trial was powered to detect a difference of 33% between the treatment groups, meaning that, small but likely clinically significant changes would escape detection.

The Role of Growth Factors in Breast Cancer

In contrast, many recent prospective studies show the association between general anesthesia and cancer metastasis and recurrence of different types of cancer. In breast cancer, vascular endothelial growth factor C(VEGF C), transforming growth factor(TGF), placental growth factor, and fibroblast growth factor promote angiogenesis and metastases. Looney, Doran, & Buggy (2010) have assessed the effects of anesthetic technique on serum concentrations of angiogenic factors associated with breast cancer by analyzing serum obtained from patients randomly assigned to receive either Sevoflurane general anesthesia with opioid analgesia or combined general anesthesia and regional anesthesia for primary breast cancer surgery. The principal findings were that VEGF C concentrations are increased after surgery in the general anesthesia group, but remain unchanged in the regional anesthesia group. On the other hand, TGF- 1 concentrations were increased after surgery in the regional anesthesia group compared with the general anesthesia group. VEGF C has been shown to be overexpressed in breast cancers, and it is an important factor in promoting angiogenesis and in aiding the dissemination of cancer cells into the systemic circulation. VEGF C may also induce paracrine signaling between breast cancer cells and the endothelium, altering the permeability of lymphatic and blood vessels.

Table 1. Anesthesia Factors and Tumor Progression

Anesthetic factors	Potential effects on tumors	Cell-mediate Immunity [7, 18]	Proposed Mechanisms
Regional anesthesia	Inhibition	Attenuate immuno-suppression	Decrease perioperative stress responses Decrease systemic opioid use Decrease the use of volatile agents
Local anesthetics	Inhibition	Attenuate immuno-suppression	Act through VGSC to inhibit metastasis [24-26] Inhibit cell proliferation [27] Inhibit motor machinery of cancer cells [28] Inhibit Src signaling and cancer cell migration [29]
Opioids	Activation	Immuno-suppression	Promote angiogenesis [30] Co-activate with EGFR [31] Act through NET1 pathway for cell migration [32]
Volatile agents	Activation	Immuno-suppression	Activate HIF-1 α [8, 33] Inhibit TNF-induced apoptosis [34] Inhibit antiapoptotic Bcl-2 down-regulation [35]
Propofol	Inhibition	None	Decrease MMP expression [36] Modulate RhoA and stress fiber for cell migration [37]

Mao, Lin, & Lin (2013)

Hypoxia-Inducible Factors (HIFs)

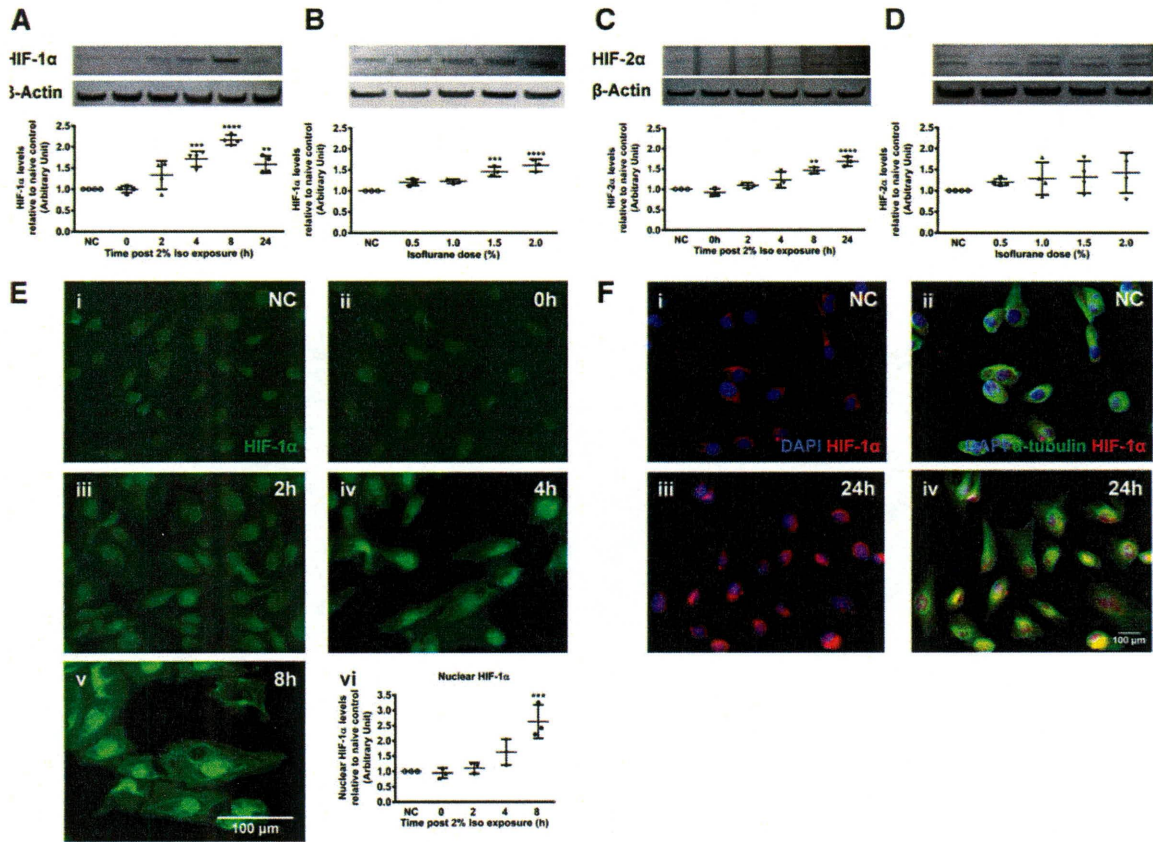
Little is known about the effect of anesthetics on cancer cells themselves. A study by Benzonana et al. (2013) found that certain anesthetics are known to affect hypoxia cell signaling mechanisms in healthy cells by up-regulating hypoxia-inducible factors (HIFs). HIFs are a family of transcription factors that regulate many of the genes involved in critical aspects of cancer activity such as cell proliferation, angiogenesis, glucose metabolism, and cell invasion. High levels of both HIF-1 α and HIF-2 α are generally detected in the majority of primary tumors and their metastases, linking high HIF levels to poor patient outcome (Benzonana et al., 2013). This study is different in that its goal was to define the effect of the commonly used volatile anesthetic Isoflurane on the HIF pathway in renal carcinoma cells, and to determine its potential impact on cancer cell behavior in terms of cell proliferation and cell migration in vitro. To evaluate this, renal cell carcinoma cells (RCC4) were exposed to 0.5–2% isoflurane for 2 hours, and then

harvested for immunoblotting and immunocytochemistry at different time points after anesthetic exposure. Immunoblotting data revealed significant increases in HIF-1 α protein levels in samples exposed to 2% Isoflurane. In addition, Isoflurane also induced HIF-1 α and HIF-2 α production in a dose-dependent manner with significant increases observed at 8-h postexposure with 1.5% and 2% Isoflurane.

Role of Isoflurane

Furthermore, Isoflurane significantly increased proliferation of RCC4 cells postexposure; Cells that allowed to migrate on tissue culture (polylysine)-coated wells were migrated significantly more when treated with isoflurane, with migration significantly increased with time in a time-dependent manner showing that there was no significant interaction between time and treatment (Benzonana et al., 2013). This study presents evidence for the first time that the volatile general anesthetic Isoflurane, an anesthetic agent commonly used in cancer surgery, stimulates a cell signaling pathway involving HIFs, which have been shown to be significant in tumorigenesis, and enhances several cellular activities associated with a malignant phenotype. In addition, it also shows that after exposure of RCC4 cells to clinically relevant concentrations of isoflurane, there is evidence of increased proliferation, cytoskeletal rearrangement, and migration of cells across different components of the extracellular matrix. Benzonana et al.(2013) also indicate that they detected statistically significantly higher levels of the proangiogenic vascular endothelial growth factor A, another factor in cancer growth. This

study adds to the evidence of anesthesia effects on cancer, this time it's the negative effect Isoflurane has, in that it enhances renal cancer cell growth .



Immunoblot and immunofluorescent analyses of hypoxia-inducible factor (HIF) changes after isoflurane exposure. Renal cell carcinoma cells were treated with or without 2% isoflurane in 21% oxygen and 5% carbon dioxide balanced with nitrogen for 2 h for time course experiments (A, C, E, and F) or with or without 0.5–2.0% for 2 h (C and D) for dose–response experiments. Time course experiments were assessed by immunoblotting against HIF-1α (A) and HIF-2α (C) and immunofluorescence of HIF-1α (E and F) at different time points (0, 2, 4, 8, and 24 h) postgas exposure. Dose–response experiments were assessed by immunoblotting against HIF-1α (B) and HIF-2α (D) 8-h postgas exposure. Exposure to isoflurane for 2 h induced HIF-1α in time-dependent (A) and dose-dependent manner (B). Expression of HIF-2α was also increased in a time-dependent (C) and dose-dependent manner (D). Furthermore, exposure to 2% isoflurane induced a time-dependent HIF-1α translocation from the cells' cytosol to the cells' nuclei (Benzonana et al., 2013).

Influence of Anesthetic Technique

A study by Wuethrich et al. (2010) also shows a potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome. According to this study, a positive effect of epidural analgesia on clinical progression-free survival was observed. In addition, no significant difference was found in biochemical recurrence free (BCR), cancer-specific, or overall survival between general anesthesia combined with thoracic epidural analgesia (TEA) and general anesthesia alone plus postoperative morphine-ketorolac analgesia in patients undergoing open radical retropubic prostatectomy with extended pelvic lymph node dissection. The authors of this study also state that regional anesthesia/analgesia is more beneficial because it attenuates the release of endogenous opioids, reduces the need for anesthetic gases, and lowers the dosage of morphine. Consequently, a less compromised immune response would be expected with a better inhibition of tumor growth and spread. Furthermore, although more fentanyl was administered to the patients in this study who did not receive epidural analgesia, the authors could not demonstrate a negative effect of the fentanyl dosage on survival. (Wuethrich et al. 2010).

Thus far, it seems like most studies confirm the positive effect of regional anesthesia alone or combined with general anesthesia or analgesia, while they show a negative effect of general anesthesia on cancer recurrence. According to Wada et al. (2007), the addition of spinal block to Sevoflurane general anesthesia reduces liver metastasis by preserving the T helper 1/T helper 2 (Th1/Th2). Wada et al. (2007) state that IFN-, a Th1 cytokine,

is known to be involved in increasing the cytotoxic activities of T cells and NK cells. On the other hand, interleukin 4 (IL-4), a Th2 cytokine, is reported to be involved in increasing humoral immunity. This study indicates that innate tumor immunity is impaired by inhibition of the cytotoxic Th1 response of liver mononuclear cells (MNCs) after lower abdominal surgery and that spinal block attenuates this impairment, thereby inhibiting the promotion of liver metastasis after surgery. In contrast, if a deeper level of sevoflurane general anesthesia was used, it could not prevent the stress response which might affect tumor cell spread, because it could not block the reflexion that originated from lower spinal level. Spinal anesthesia, however, could block or blunt it, hence the effect of combining the two.

Effects of Epidural Use

A meta-analysis by Chen & Miao (2013) also suggests a beneficial effect of epidural use on the overall survival after cancer surgery, especially for colorectal cancer. However, according to the results, epidural use did not further decrease the recurrence events of cancer, but it might rather be associated with improved overall survival in patients with operable cancer surgery. Besides reports in cancer surgery, meta-analyses of randomized clinical trials and population-based cohort studies of other surgeries have also demonstrated that neuraxial anesthesia might reduce mortality as well as other serious complications when compared with general anesthesia. Moreover, as mentioned previously, the authors also suggest that epidural anesthesia is superior to general anesthesia in shifting the Th1/Th2 balance towards Th1, which could benefit

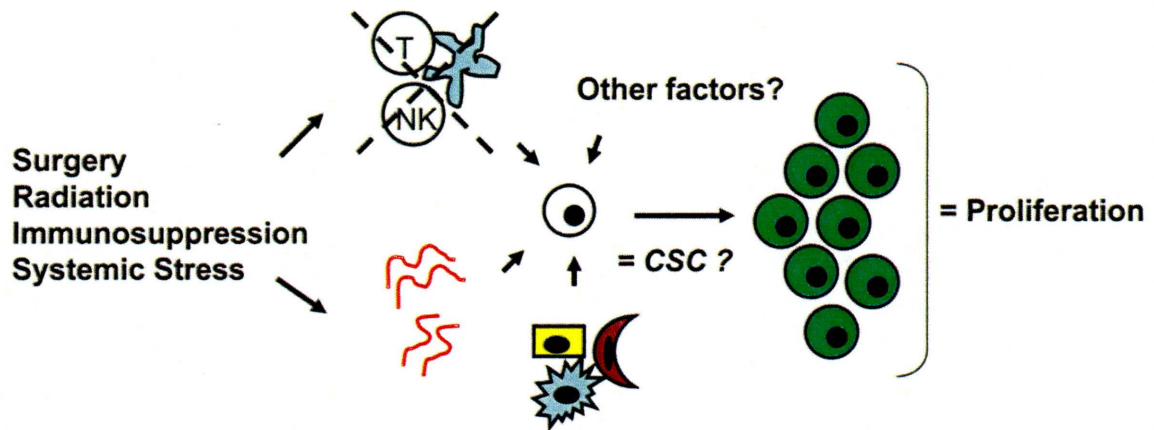
hepatocellular carcinoma patients by promoting anti-tumor Th polarization (Chen & Miao, 2013).

Effects of Volatile and Intravenous Anesthetics

There are limited studies on the effects of volatile and intravenous anesthetics on cancer. According to Mao, Lin, & Lin (2013), with the exception of propofol, volatile and intravenous anesthetics are known to depress all aspects of immunity system, which further increases the surgically-induced immunosuppression. Isoflurane is found to protect colon cancer cells from tumor necrosis factor (TNF)-induced apoptosis, while it attenuates neurotoxicity imposed by opioid peptide in neuroblastoma cells. Animal studies suggest that halogenated volatile anesthetics are organ-protective against ischemia, but this effect may be detrimental in the context of cancer. This is because halogenated volatile anesthetics up-regulate the expression of hypoxia-inducible factor 1 α (HIF-1 α) in the heart and brain under hypoxic conditions. HIF-1 α is over-expressed in a variety of carcinomas and their metastases such as in breast cancer.

In a very early study in mice, nitrous oxide has been shown to be associated with accelerated development of post-surgical metastasis in the lung and liver. However, a recent randomized follow-up study finds no increased risk of recurrence in 4-8 years after colorectal cancer surgery in patients who have received nitrous oxide. In contrast, propofol may have a beneficial anti-tumor effect by promoting cytotoxic T lymphocyte activities and inhibiting lymphoma growth. The authors also state that propofol also decreases the expression of extracellular matrix protein and the invasiveness of colon

cancer cells. Mao, Lin, & Lin (2013) state that ketamine is the most potent intravenous anesthetic agent for lung cancer metastasis in animal models, and it's mainly due to its strong immunosuppressive effects.



Surgery and other stimuli may affect angiogenesis and immune regulation, which in combination with other local microenvironment factors (e.g., pre-metastatic niche cells), promote escape from tumor dormancy leading to tumor cell proliferation (green). The relationship of dormant tumor cells to cancer stem cells (CSC) remains to be elucidated.

Tseng, Fadaki, & Leong (2011).

Cytokines

Chen & Miao (2013) note that cytokines such as IL-2, IL-12, and IFN- γ are suppressed during surgery. Consequently, the number of circulating NK cells, cytotoxic T-lymphocytes, and the ratio of T-helper 1 to T-helper 2 are significantly reduced. This immunosuppression increases the risk of malignancy and dispersed tumor emboli during surgery. Intraoperative use of regional anesthesia reduces this immunosuppression by lowering plasma levels of cortisol and catecholamines, which in result helps maintain NK function and cellular immunity.

Future Studies

It is important to note that despite the numerous studies indicating a correlation--whether positive or negative--between anesthesia and cancer recurrence, prospective studies and controlled clinical trials are desperately needed to evaluate the impact of each individual anesthetic on cancer recurrence and long-term patient survival.

It is not enough to stress how critical general anesthetics are, especially being the sole class of drugs used by physicians for inducing unconsciousness. Even though our understanding of these drugs have evolved tremendously, there is always more research to be done in order to get more definitive answers about their mechanism of action and side effects. As Mashour, Forman, & Campagna (2005) stated, “the fundamental mystery of general anesthesia will always be inextricably linked to the fundamental mystery of consciousness” (p.360). As mentioned previously, general anesthesia is a process of cognitive unbinding, and research has shown that main processes in consciousness are affected by general anesthetics. Furthermore, it is now clear that there is a relation between sleep, coma, and anesthesia, so a better understanding of these concepts might consequently result in new approaches to general anesthesia and the alteration of consciousness. General anesthetics have traditionally been considered to be non-specific drugs. However, molecular pharmacology and transgenic animal studies are revealing that they are in fact quite selective for important CNS targets and structures that are critical for modulating the processes associated with consciousness. Overwhelming evidence points to the activity of the majority of anesthetics at ligand-gated ion channels, providing an excellent rationale for their physiological effects. Enhancement of inhibitory function via GABA and/or glycine or background potassium channels, or inhibitions of excitatory pathways, such as NMDA are clearly providing hard targets and testable hypotheses. As mentioned above, understanding the mechanisms of action of these three groups have led to a better clinical application of general anesthetics; this explains why

today, a combination of drugs is used in order to achieve different results, as opposed to just one drug. Due to all the advances in biological techniques, new avenues are being opened; and it's expected see a combination of these techniques along with transgenic technology to provide definitive answers to the role played by different ion channels in anesthesia, as well as the side effects of currently used drugs (Thompson & Wafford, 2001).

Furthermore, it is important to mention that most studies performed so far show that although the majority of clinically used general anesthetics have been shown to induce developmental neurodegeneration, it seems that the timing and duration of anesthesia exposure are very important factors, suggesting that age, rather than the choice of anesthesia, may be the main risk factor in anesthesia-induced developmental sequelae. On the other hand, not only there isn't enough research about this issue, but also, most studies so far have been retrospective. No studies to date have used directly administered neuropsychological assessments as outcome measures, except for the study mentioned previously by Ing et al.,(2012). Thus far, this study seems to be the only one that analyzes the association between early exposure to anesthesia and neurocognitive deficits by using a battery of directly administered neuropsychological assessments.

Although the lack of information and research makes it too early to tell what implications these findings may have on pediatric anesthesia practice, it is of paramount importance to relentlessly pursue a better grasp of poor neurocognitive outcomes that could be anesthesia-induced (Wang, Xu, & Miao, 2014). It is essential to have more studies

performed on a recent cohort which includes children who were born in the last 10 years. Anesthesia agents have changed greatly since the cohorts used in the studies mentioned above, which is another limitation to consider. Furthermore, since the use of anesthetics in obstetric and pediatric anesthesia is a necessity that cannot be avoided when pregnant mothers and newborn infants present with life threatening conditions requiring surgery or a prolonged sedation, it is imperative that we improve our understanding of the mechanisms that underlie the neurotoxicity of anesthetic agents.

Thus far clinical evidence indicates a positive effect on cancer prognosis for regional anesthesia, local anesthetics and propofol, however, it suggests the opposite effects for inhalational and intravenous anesthetics. General anesthetics are immunosuppressive and increase susceptibility to tumor progression.

As of 2013, only one major prospective randomized-control clinical trial has been published on the long-term impact of anesthetic technique and postoperative cancer recurrence. The trial randomized oncologic patients undergoing major abdominal surgery to receive general anesthesia with either epidural or opioid analgesia. No significant difference was detected in cancer free survival; this result might not be completely reliable due to the fact that the amount of volatile anesthetic was not recorded and may represent a significant confounding variable.

It is important to note that despite the numerous studies indicating a correlation--whether positive or negative--between anesthesia and cancer recurrence, prospective studies and

controlled clinical trials are desperately needed to evaluate the impact of each individual anesthetic on cancer recurrence and long-term patient survival.

New Research

For the first time since the 1970s, University of Pennsylvania researchers have developed a new technique for identifying potential compounds, which may lead to the next generation of anesthetic drugs. According to Roderic G. Eckenhoff, M.D. (2015), lead author of the study and professor of Anesthesiology and Critical Care at the Perelman School of Medicine at the University of Pennsylvania, usually researchers modify existing anesthetic drugs, rather than develop an entirely new class of anesthetics. Eckenhoff and his team sought to prove that a new approach could reveal completely new anesthetic structures. Their approach, often used in drug development for therapeutics, but never before with anesthetics, identified two new anesthetic drugs that have the potential to be used on humans.

The researchers used a screening process that allowed them to test over 350,000 compounds for their potential to serve as anesthetic agents, in collaboration with the Chemical Genomics Center of the National Center for Advancing Translational Sciences (NCATS). The compounds were tested for their ability to bind a surrogate anesthetic binding protein target, apoferritin. Among the 350,000, researchers found 2,600 compounds that had strong interactions with apoferritin. A subset of the 2,600 were chosen based on structural criteria to be tested for anesthetic activity, first on tadpoles and then on mice, an effort performed by Andrew McKinstry-Wu, M.D.(2015), an

instructor in the department of Anesthesiology and Critical Care. The researchers concluded that two compounds could potentially serve as anesthetics.

Eckenhoff (2015) stated that while the safety of anesthesia have improved over the years, there are still many risks associated with it , and no new anesthetics have been developed for more than 40 years.

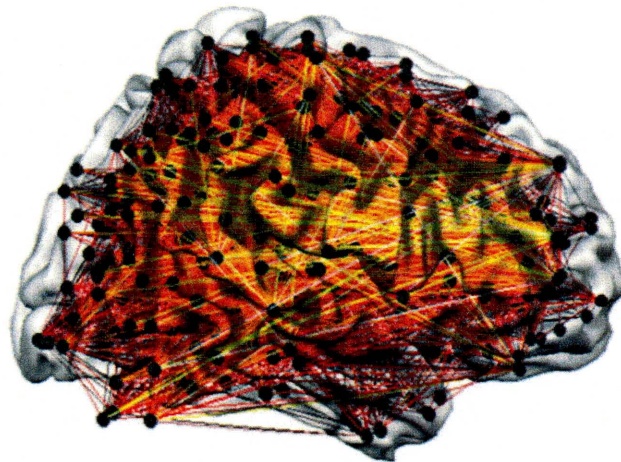
Furthermore, he added that “the anesthetics identified by this approach require further development before they can be considered for use in the O.R. However, the study results show that novel anesthetics do exist, and that we need not restrict ourselves to small modifications of existing drugs.”

This year as well, Vanderbilt University Researchers Godwin, Barry, and Marois (2015) discovered global changes in how brain areas communicate with one another during awareness. Their findings, which were published on March 9th, 2015 in the Proceedings of the National Academy of Sciences, challenge previous theories that hypothesized much more restricted changes were responsible for producing awareness. Using graph theory, a branch of mathematics concerned with explaining the interactive links between members of a complex network, such as social networks or flight routes, the researchers aimed to characterize how connections between the various parts of the brain were related to awareness. “With graph theory, one can ask questions about how efficiently the transportation networks in the United States and Europe are connected via transportation hubs like LaGuardia Airport in New York,” Douglass Godwin(2015), graduate student and lead author on the research, said. He added that the same questions

about brain networks and hubs of neural communication can be asked. Modern theories of the neural basis of consciousness fall generally into two camps: focal and global. Focal theories contend there are specific areas of the brain that are critical for generating consciousness, while global theories argue consciousness arises from large-scale brain changes in activity. This study applied graph theory analysis to adjudicate between these theories. The researchers recruited 24 members of the university community to participate in a functional magnetic resonance imaging (fMRI) experiment. While in the fMRI scanner, participants were asked to detect a disk that was briefly flashed on a screen. In each trial, participants responded whether they were able to detect the target disk and how much confidence they had in their answer. Experimenters then compared the results of the high-confidence trials during which the target was detected to the trials when it was missed by participants. These were treated as “aware” and “unaware” trials, respectively.

Unlike previous studies, the present study, was interested not simply in what regions might be more activated with awareness, but how they communicate with one another. The results via this network approach pointed toward a different conclusion. No one area or network of areas of the brain stood out as particularly more connected during awareness of the target, but the whole brain appeared to become functionally more connected following reports of awareness. Marois (2015) states that there are numerous brain networks that control distinct cognitive functions such as attention, and language

and control, with each node of a network densely interconnected with other nodes of the same network, but not with other networks. He added that “Consciousness appears to break down the modularity of these networks, as we observed a broad increase in functional connectivity between these networks with awareness.” This study suggests that consciousness is likely a product of this widespread communication, and that we can only report things we see once they are being represented in the brain in this manner. The authors state that “no one part of the brain is truly the ‘seat of the soul,’ as René Descartes once wrote in a hypothesis about the pineal gland, but rather, consciousness appears to be an emergent property of how information that needs to be acted upon gets propagated throughout the brain.” Godwin (2015) adds that humans don’t experience separate visual and auditory worlds, but rather it’s all integrated into a single conscious experience through widespread cross-network communication.



The black dots correspond to the 264 areas of the cerebral cortex that the researchers probed, and the lines correspond to the increased strength of the functional connections between each of these brain areas when subjects consciously perceive the target. The "hotter" colors are associated with stronger connections. This figure illustrates that awareness of the target corresponds to widespread increase in the strength of functional connections (Godwin, Barry, Marois, 2015).

Conclusion

Conducting this literature review resulted in expanded knowledge and insight in the areas of consciousness, general anesthetics, and their effects. The topic of anesthesia encompasses a body of growing knowledge. Thus, targeting further research related to the effects of anesthesia on human development and cancer prognosis was an important outcome of this investigator's literature review.

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