THE NEURAL MECHANISMS OF GENERAL ANESTHESIA

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ABSTRACT

THE NEURAL MECHANISM OF GENERAL ANESTHESIA

Zarith Fadila bt Jamel

This study aims to analyze, assess and synthesize other research works on the neural mechanism of general anesthesia. The main focus of this study is to investigate the region of the brain involved in the induction of general anesthesia and the neural mechanisms of general anesthetics that induce general anesthesia, based on the experiments and primary research carried out by other researchers. The results of experiments and findings from other researchers are gathered and analyzed to see how the results of the experiments may conform or contradict each other. The parts of the brain involved in general anesthesia are identified. The neural mechanism of general anesthesia is better understood as well. From the extensive discussions in this research, it is found that thalamus, brainstem and reticular formation are the main targets of anesthetics. In terms of neural mechanism, general anesthetics exert its actions by altering neural functions and activities, causing the signal in the brain to be desynchronized.
ABSTRAK

MEKANISME NEURAL ANESTHESIA UMUM

Zarith Fadila bt Jamel

1.0 Introduction

Each year, over 21,000,000 people receive general anesthesia. The vast majority go to sleep peacefully. They remember nothing… 30,000 of these patients are not so fortunate. They find themselves unable to sleep. Trapped in a phenomenon known as anesthesia awareness.

(Awake, 2007)

The above quote was taken from the movie Awake (2007). This movie features the topic of interest in this research, the general anesthesia procedure. Clayton, a heart patient, was undergoing a heart transplant when he could not sleep, could not move and was aware of his environment. Everyone in the operation theatre did not know that he was still awake when they started to cut through his body. He was forced to go through the unbearable pain where he could not move and do anything as he was totally and temporarily paralyzed. However, his memory was still functioning as he could remember some events in his life. Overall, although it was successful in putting the patient into immobility, the procedure did not achieve its other goals as he was still conscious, has memory or recall of events and has pain.
Figure 1: Clayton being given anesthetics before surgery (Awake, 2007)

Figure 2: Ten seconds after being given anesthetics (Awake, 2007)

Figure 3: During surgery (Awake, 2007)
Figure 1, Figure 2 and Figure 3 show Clayton being given anesthetics before the surgery, ten seconds after being given anesthetics and his condition during the surgery. This procedure is an example of general anesthesia and is similar in any surgeries carried out globally.

Every year, approximately 45 million patients undergo common surgeries in United States of America alone (Resource 4 Surgical Accidents, 2006). Some may undergo minor surgeries while some are required to undergo major operations. Whether the operations or surgeries are minor or major, the patients will need to go through anesthesia or anaesthesia. In this project, we will only use the term anesthesia so as not to confuse unfamiliar readers. From medical point of view, anesthesia is defined as a general or local insensibility, as to pain and other sensation, induced by certain interventions or drugs to permit the performance of surgery or other painful procedures (Medline Plus, 2005).

Basically, there are four types of anesthesia, which are general anesthesia, regional anesthesia, monitored anesthesia care and local anesthesia (Tallgrass Anesthesiology Associates, 2007). If given a general anesthesia, a patient will be totally unconscious so that she will not feel, see or hear anything during the surgical procedure after being given anesthetic medications through an intravenous line or through an anesthesia mask (Tallgrass Anesthesiology Associates, 2007). Regional anesthesia on the other hand, causes the patient to feel numb at the part of body that is going to be operated after being given the injection of local anesthesia around nerves in a region of the body corresponding to the surgical procedure. For patients who undergo surgeries with regional anesthesia, they will feel comfortable, drowsy and their memories are blurred (Tallgrass Anesthesiology Associates, 2007). As for monitored anesthesia care, the patients usually receive pain medication and sedatives through her intravenous line from her anesthetist. The anesthetist will inject local anesthesia into the skin, which will provide additional pain control during and after the procedure. The anesthetist will also be responsible in monitoring the patient’s vital body functions during the procedure (Tallgrass Anesthesiology Associates, 2007). Local anesthesia is almost similar to regional anesthesia as they are used to produce insensitivity to an area of the body so a surgeon can do work on patient while they are awake (Larkin, 2008).
However, it is different from regional anesthesia because the area that is involved in local anesthesia is relatively smaller than the area in regional anesthesia. Local anesthesia is more common than regional anesthesia as they are used for common treatments and as painkillers (Larkin, 2008). An example of local anesthesia application is the field of dentistry where it is beneficial for the patient to position their mouth and vocalize any problems. The nerves of a few teeth will be numbed by an injection of local anesthesia before light drilling and other minor procedures (Larkin, 2008).

As stated earlier, there are patients who undergo minor or major surgeries. Patients undergoing minor surgeries will be given regional anesthesia, which means that the patient will be injected with anesthetics at the part of body that is going to be operated. Regional anesthesia involves only some part of the body and does not cause the patient to fall into total unconsciousness. General anesthesia, on the other hand, will cause the patients to fall into total unconsciousness by using interventions or anesthesia masks. In this project, we will be focusing only on general anesthesia.

Even though anesthesia procedure has been performed for hundreds of years, the real mechanism of it is still not completely answered. How it actually causes the patients to fall into unconsciousness in a matter of minute is still a mystery amid the thousands of research done by researchers who came out with different points of view, all of whom who run different kind of techniques and methods in order to find answer to one great question, “How does anesthesia cause unconsciousness?” In order to unravel the mystery, the term consciousness itself needs to be understood. Yet, this is another term that defies definition. Thus, up to these days, researchers are still coming out with different theories, trying to explain the problems regarding anesthesia and consciousness.

The early studies of the real mechanism of anesthesia can be tracked back to the years of Francois Magendie (1783-1855), a French physiologist who studied the mechanisms of anesthetic drugs, which leads the next generation of physicians to follow his footsteps. Among his findings were the conclusions that poison worked most quickly when placed directly on the spinal cord or brain rather than on a peripheral nerve, and that the onset of
action varied directly with the time it took for the drug to reach the brain. The example for the latter finding is when an intravenous injection killed more rapidly than intra-muscular injection (Caton & Antognini, 2003). Besides that, he also asserted that “The circulation had to be intact for poison to work. Dogs died quickly after an injection of the poison into a severed limb, but only when he left its arterial and venous connections intact” (p. 4).

However, Magendie’s experiments did not leave a big impact on the practical American physicians who first demonstrated the anesthetic effects of nitrous oxide and ether. Physicians such as Long, Wells and Morton were totally different from Magendie in terms of their interest where they were more interested in relieving pain only, rather than the mechanisms of anesthesia. Physicians who had common interest with Magendie were mostly from Europe (Caton & Antognini, 2003).

Another French physiologist, Pierre Flourens described anesthesia as a progressive depression of the nervous system beginning with the cortex, followed by the cerebellum, and finally the brain stem and spinal cord. His description of anesthesia was agreed upon by Nicolai Pirogoff (Caton & Antognini, 2003).

Pirogoff was among the early physicians who developed the early concepts of mechanisms of anesthesia and its site. Pirogoff’s work revolved around explaining how ether blocked the conduction of impulses. He then suggested two possibilities. First, ether might have some “chemical action on nervous tissue” and secondly, he thought that “ether vapor in the capillary system surrounding nervous tissue” might exert a “greater or lesser degree of compression on the component fibers of the brain and nerves, partly by the force of expansion or partly by passage into the cerebrospinal fluid” (Caton & Antognini, 2003, p. 5).

In 1855, Alexander Wood introduced hypodermic injections following the debate on the primary site of action of morphine. Most believed that it affected the brain, while others believed that morphine had its most profound effect on peripheral nerves (Caton & Antognini, 2003).
Magendie’s student, Claude Bernard was next to step up with his work where he defined anesthesia and distinguished it from narcotism, a state that he associated with morphine. He also sought to explain anesthesia in precise anatomical and physiological terms. Other than that, he was also interested in studying the primary site of action of anesthetic drugs. Like Magendie and Pirogoff, Bernard concluded that anesthetics act on brain rather than peripheral nerves (Caton & Antognini, 2003).

Another early contributor to the development of anesthesia studies was English physician, John Snow. Snow was particularly different from other physicians where he was among the first to establish a quantitative relationship between the concentration of inspired gas and the clinical response. He manipulated the different concentrations of anesthetics and used small animals as the specimens. Snow then used the data to argue for more precise control over concentrations of ether administered to patients (Caton & Antognini, 2003).

Researchers discussed above are among the thousands of physicians interested in investigating the mechanism of anesthesia and its site. Up to these days, the works of these prominent researchers are used as the base and foundation of the field, which are still carried out and continued by researchers of the new generation in order to answer the question of “How does anesthesia cause unconsciousness?”

1.1 Problem Statement

From the literature review, it is found that meta-analysis works on cognition and anesthesia are sparse. In fact, none of the meta-analysis works reviewed focused specifically on the neural mechanism of general anesthesia.

For instance, a meta-analysis on memory for events during anesthesia was done by Merikle and Daneman (1996). Meanwhile, Ritchie, Polge, Roquefeuil, Djakovic and Ledesert (2005) were more interested in studying the impact of anesthesia on the cognitive functioning of the elderly. Liu, Strodtbeck, Richman and Wu (2005) on the other hand performed a meta-analysis that compared regional anesthesia and general anesthesia.
Subsequently, Tramer, Moore and McQuay (1996) gave a review on the effectiveness and safety of anesthetics which omitted nitrous oxide (N2O) to prevent postoperative nausea and vomiting (PONV).

Thus, from the literature review, it is clear that meta-analysis works on anesthesia are sparse and they are more medical in nature. Therefore, it appears that none of these studies are discussing on the neural mechanism of anesthesia. Hence, this project aims to tackle the problem of neural mechanism of general anesthesia by analyzing and synthesizing the opinions of researchers in anesthesia.

1.2 Objectives

The purpose of this study is to investigate further the nature of anesthesia from the neuroscience perspective. More specifically, this project tries to analyze, to assess and make a synthesis out of the primary research and other meta-analyses works on anesthesia and consciousness. This project will focus on general anesthesia and the neural process underlying general anesthesia, the sites or targets of anesthetic actions, its relationship with consciousness and current research on anesthesia that apply different approaches.

1.3 Significance of Study

It is hoped that this project would help address the relative absence of meta-analysis works on neural mechanism of general anesthesia and consciousness. By doing so, it is also hoped that this project would make a worthwhile contribution to the field of cognitive neuroscience.

1.4 Literature Review

Basically, the literature review of this project is done by reviewing meta-analysis works conducted by past researchers. Cognition in human beings usually refers to processes such as thinking, perceiving, imagining, speaking, acting and planning (Ward, 2006). A meta-
analysis on memory for events during anesthesia was done by Merikle and Daneman (1996). Merikle and Daneman found that there is considerable evidence of memory for specific information presented during anesthesia, provided that the memory test is administered within 24 hours following surgery. This was shown by the strongest evidence of memory for events during anesthesia that had been found in those studies that carried out the memory tests at the shortest time following surgery, while the patients were still in the recovery room as soon as they gained consciousness. This evidence can also be strengthened by the findings that when the memory tests were delayed two or more days following surgery, there was little evidence of memory for any specific information presented during anesthesia.

Apart from that, meta-analysis had also been done to study the impact of anesthesia on the cognitive functioning of the elderly. Ritchie, Polge, Roquefeuil, Djakovic and Ledesert (2005) collected literatures using five bibliographic databases, which are PASCAL, Medline, Excerpta Medica, Psychological Abstracts and Science Citation Index. They found that significant cognitive dysfunction was common in elderly persons one to three days after surgery. However, reports of longer-term impairment were inconsistent due to the heterogeneity of the procedures used and populations targeted in such studies. Incidence rates vary widely according to type of surgery, suggesting that factors other than anesthesia explain a significant proportion of the observed variance. Above all, anesthesia appears to be associated with longer-term cognitive disorder and the acceleration of senile dementia, but only in a small number of cases, suggesting the existence of other interacting etiological factors.

Besides the resources discussed above, there are also a number of meta-analysis done in the medical field.

In 2005, Liu, Strodtbeck, Richman and Wu conducted a meta-analysis to make a comparison between regional anesthesia and general anesthesia for ambulatory anesthesia. Ambulatory can be defined as the ability to walk about and is not bedridden (MedlinePlus, 2005). Thus, in the context of ambulatory anesthesia, a patient will be able to recover well and lead a normal life after surgeries in a faster rate. This is supported by Tallgrass
Anesthesiology Associates (2007) where this organization states that ambulatory anesthesia is tailored to meet the needs of ambulatory surgery so the patient can go home soon after her operation. In completing the meta-analysis, the researchers looked up into the National Library of Medicine’s Medline database and the Cochrane Database of Systematic Reviews and collected materials from 1966 to April 2005 where 214 materials were identified as potential randomized controlled trials (RCTs). However, only 15 trials for central neuraxial blocks (CNB) consisting of 1003 patients and 7 trials for peripheral nerve blocks (PNB) consisting of 359 patients were included in the meta-analysis. As a result, the meta-analysis found that regional anesthesia has several potential advantages over general anesthesia such as decreased postanesthesia care unit use, nausea and postoperative pain.

In 1996, Tramer, Moore and McQuay ran a meta-analysis to assess the effectiveness and safety of anesthetics which omitted nitrous oxide (N₂O) to prevent postoperative nausea and vomiting (PONV). 24 reports with information on 2478 patients were studied where early and late PONV (6 and 48 hours after operation, respectively) and adverse effects were evaluated using the numbers-needed-to-treat (NNT) method. The findings from this meta-analysis was after the omission of N₂O from general anesthetics, postoperative vomiting is significantly decreased. Omitting N₂O does not affect nausea or complete control of emesis. However, they concluded that there is still no evidence that omitting N₂O is more effective in propofol than in halogenated anesthetics. They also stated that the clinically important risk of intraoperative awareness with a N₂O-free anesthetic reduces the usefulness of this method of preventing postoperative vomiting.

Meanwhile, Sorenson and Pace (1992) were interested to investigate the most suitable anesthetic technique for surgeries to repair femoral neck fractures in older women. There is a difference of opinion as to the choice of regional versus general anesthesia for surgery in these patients. Thus, Sorenson and Pace conducted a meta-analysis to compare the survival of patients with traumatic femoral neck fractures undergoing operative repair during regional or general anesthesia. 13 randomized controlled trials (RCTs) were identified. The meta-analysis however, does not allow a conclusion that important differences in mortality exist between regional and general anesthesia for traumatic hip fracture.
Hence, there appears to be a gap in the literature which forms the basis of the present study, the neural mechanism of anesthesia.

1.5 Research methodology

Basically, this project is qualitative in nature and to complete this project, reading and analysis of numerous research studies done by past researchers will be needed. Main materials can be found in books available in Centre for Academic Services (CAIS) of UNIMAS and the Faculty of Medicine and Health Science. Apart from that, materials from journals and websites will also be used. It is hoped that from the analysis of these various materials, a synthesis can be made and contributions could be made to the field.

1.6 Scope and limitation

This project will narrow its scope to general anesthesia. This is done because anesthesia comes in various types and it is impossible to cover all types of anesthesia. Apart from that, this project is mainly concerned with the neural mechanism of anesthesia. Thus, only general anesthesia provides a view into the neural mechanism as it involves unconsciousness, which could not be found in other types of anesthesia. Another reason is the brain activity is observable during the procedure of general anesthesia and this meets the criteria of this project where the mechanism is viewed from neuroscience perspective.

The limitation of the study would come from the insufficient materials available in the library. Books on anesthesia rarely can be found in CAIS and in order to compensate for this disadvantage, books on anesthesia are obtained from the medical faculty. Besides that, time given is extremely limited and this constraint limits any further investigation of this project.
1.7 Conclusion

Therefore, by completing this study, the ambiguity of the neural mechanism of general anesthesia can be explained in detail, thus strengthening the understanding of how general anesthesia causes unconsciousness. It is also hoped that this study will be able to help future researchers and students to understand and build interest in this field.
2.1 Introduction

Human brains are such a unique organ as it is able to work in a mysterious manner to raise experience in higher-order mammal especially human beings. The small, wrinkled organ is even more complex than the most complex and complicated computer. Neuroscientists have always been trying to solve problems pertaining to the brain and its components. The four Ws and 1 H (what, where, why, when and how) can best describe the components that the researchers are interested in. Interests are built in what a brain is, where those events occur in brains, why does an event occur, when is an event occurring and how the event occurs in the brain. These are all the questions that they look into through experiments and researches.

The brain enables our minds to see, hear, remember, think, feel, speak, and dream. Neuroscientists even say that the mind is what the brain does (Myers, 1999). Thus, what the brain does is manifested through our actions. The same applies to patients who are given anesthetics, where actions of the drug in the brain are manifested through the unconsciousness of the patient. The brain constitutes one over 45 of the body’s weight (Myers, 1999) or about 2% of body weight (Ward, 2006).

Human nervous system is important in order to enable humans to function normally. Without nervous system, they will be in a great ‘danger’ as they are unable to response to environment. Basically, human nervous system is about the communication system, in which the most basic unit called neuron or nerve cells communicate with each other. In other words, the nervous system is human body’s primary information system, where neurons communicate with other neurons (Myers, 1999).