The effect of general anesthesia on the quality of sleep

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Abbreviations

Abbreviation	Explanation
ASA	American Society of Anesthesiologists
PACU	postanesthesia care unit
CNS	central nervous system
GABA	γ-aminobutyric acid
MAC	minimal alveolar concentration
ICU	intensive care unit
$GABA_A$	γ-aminobutyric acid type A
NMDA	N-methyl-d-aspartate
NREM	non-rapid eye movement
REM	rapid eye movement
EEG	electroencephalogram
SWS	slow wave sleep
VLPO	ventrolateral preoptic nucleus
SCN	suprachiasmatic nucleus
BMAL1	brain and muscle ARNT-like 1
CLOCK	circadian locomotor output kaput
PSQI	Pittsburgh sleep quality index

Contents

Summary

Title: The effect of general anesthesia on the quality of sleep

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General anesthesia is a procedure performed every day worldwide due to numerous surgical and nonsurgical indications. It produces pronounced changes in the patient's body homeostasis, primarily due to the drugs used to achieve the state of general anesthesia. The most frequent components of general anesthesia are various sedative, analgesic and hypnotic drugs, all of which exert their effects through acting on receptors in the central nervous system. The effects produced by these drugs are essential to the basic characteristics of the state of general anesthesia. However, it is evident that some of the effects of general anesthesia surpass the time actually spent in the state of general anesthesia. The effects of general anesthesia on the quality of sleep is of particular interest in this matter and has received increasing attention over the past few decades, thus becoming the topic of numerous researches. As general anesthesia is most commonly utilized to enable performing various surgical procedures, one of the greatest challenges in testing how general anesthesia affects the quality of sleep is in separating the effects on sleep produced solely by general anesthesia from the effects produced by surgical procedures and in hospital stay (tissue trauma, pain, intensive care unit environment, etc.). It is why animal studies have proven useful in providing conditions difficult to replicate in human studies due to both practical and ethical reasons and therefore comprise a significant fraction of studies related to this topic. Although fewer in numbers, human studies have been performed and are of great value in better understanding the answers to questions related to general anesthesia's influence on sleep. Both animal and human studies, although diverse in the particular focus of each study, confirm that general anesthesia not only produces a state comparable to sleep in more than just appearance, but may even satisfy the need for certain stages of homeostatic sleep. The studies also agree that general anesthesia greatly influences the quality of sleep in the postanesthetic period. The magnitude and length of this influence are dependent on many factors, including the choice of drugs utilized to achieve the state of general anesthesia and the time of day at which the procedure is set and may last for days and even months. As sleep is a vital component of quality of life and is essential for achievement of optimal function of various organ systems, it is not surprising that it is also a key element of postoperative recovery. Further research in this area is required to better understand this topic and to add to better understanding of general anesthesia, as well as improving patients' quality of life in a long-term manner.

Keywords: general anesthesia, sleep, circadian rhythm

Sažetak

Naslov: Utjecaj opće anestezije na kvalitetu spavanja

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Opća anestezija je vrsta je anestezije koja se izvodi svakodnevno diljem svijeta zbog brojnih kirurških i ne kirurških indikacija. Ona uzrokuje značajne promjene homeostaze pacijenta, prvenstveno zbog lijekova kojima se postiže stanje anestezije. Najčešće korišteni anesteziološki lijekovi su sedativi, analgetici i hipnotici, a njihovi su učinci rezultat djelovanja na receptore u središnjem živčanom sustavu. Djelovanje ovih lijekova ključno je za postizanje osnovnih karakteristika stanja opće anestezije. Međutim, neki od učinaka opće anestezije nadilaze vrijeme provedeno u stanju opće anestezije. Posebno zanimljiv je učinak opće anestezije na kvalitetu spavanja. Tijekom posljednjih nekoliko desetljeća ovoj temi se posvećuje sve više pozornosti, čime ona postaje predmet mnogih istraživanja. Budući da se opća anestezija najčešće primjenjuje da se omogući izvođenje raznih kirurških zahvata, jedan od najvećih izazova u proučavanju utjecaja opće anestezije na kvalitetu spavanja je razlučiti utjecaj same opće anestezije od utjecaja kirurškog zahvata i boravka u bolnici (trauma tkiva, bol, uvjeti u jedinici intenzivnog liječenja). Upravo zato su se studije na životinjama pokazale korisne u omogućavanju uvjeta koje je, iz praktičnih i etičkih razloga, teško osigurati kod studija na ljudima i čine značajan dio studija povezanih s ovom temom. Iako postoje u manjem broju, studije na ljudima vrlo su vrijedan dio boljeg razumijevanja utjecaja opće anestezije na san. Obje vrste studija, iako im se specifični fokusi razlikuju, potvrđuju kako opća anestezija, osim što uzrokuje stanje slično snu, potencijalno zadovoljava potrebu za određenim fazama homeostatskog sna. Studije također ukazuju na to da opća anestezija značajno utječe na kvalitetu sna u poslijeanestezijskom razdoblju. Značaj i trajanje tog utjecaja ovise o mnogim čimbenicima, koji uključuju izbor lijekova kojima se postiže stanje opće anestezije i doba dana tijekom kojeg se opća anestezija izvodi, a utjecaj može trajati danima, čak i mjesecima. Uzimajući u obzir da je san ključna komponenta kvalitete života i nužan je za optimalno funkcioniranje raznih organskih sustava, nije iznenađujuće kako je također ključan čimbenik poslijeoperativnog oporavka. Kako bi se navedene teme bolje razumjele potrebna su daljnja istraživanja. Njihovo razumijevanje bi doprinijelo dugoročnom poboljšanju kvalitete života pacijenata, a i boljem razumijevanju učinaka opće anestezije.

Ključne riječi: opća anestezija, spavanje, cirkadijani ritam

1. General anesthesia

General anesthesia is a drug-induced state of unconsciousness characterized by amnesia, analgesia, inhibition of autonomic reflexes and skeletal muscle relaxation (6). During this state patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired (1).

The course of general anesthesia begins in the preoperative period. General anesthesia requires a thorough preoperative evaluation. This includes evaluation of the patient's medical history and performing physical examination. The preoperative evaluation is the key to constructing the anesthetic plan and if inadequate is associated with anesthetic complications. Another purpose of this evaluation is to provide an estimate of anesthetic risk, which can be expressed through various scoring systems, the most utilized being the American Society of Anesthesiologists (ASA) classification (2, 3).

The primary focus of evaluating the patient's medical history is cardiac and pulmonary function, kidney disease, endocrine and metabolic diseases, as well as anatomical and musculoskeletal issues that may be relevant to airway management. Attention should also be directed to any previous exposure to anesthetics and subsequent reactions, allergies to drugs and other substances and any medication taken by the patient recently or at the present time (2).

The basic elements of performing a physical examination on a healthy, asymptomatic patients include measurement of vital signs (blood pressure, heart rate, respiratory rate, and temperature) as well as examination of the heart, lungs, and musculoskeletal system by utilizing techniques such as inspection, auscultation, palpation, and percussion. In addition, the patient's airway and dentition should be examined before every anesthetic procedure.

The focus and the specifics of the physical examination are tailored to the individual needs and medical conditions of each patient. Additional elements can be added to the physical examination and are based on the patient's medical history or identification of potential risk factors (2, 3).

The intraoperative period of a general anesthesia consists of induction, maintenance and emergence (4).

Upon arrival to the operating theatre, it is essential to ensure adequate patient monitoring. Basic monitoring includes continuous evaluation of oxygenation, ventilation, circulation and temperature via pulse oximetry, capnography, electrocardiography, blood pressure cuff and

temperature probe respectively. Based on the type of procedure and the patient's medical history and present status, additional monitoring can be applied (2, 10).

Prior to induction, many patients receive premedication consisting of one or more drugs that reduce anxiety, provide analgesia, prevent post-operative nausea and vomiting and if needed reduce the perioperative risk to the patient. An example of a commonly used premedication is midazolam, given orally or intravenously to adults and as a syrup to the pediatric population, which in addition to its sedative effects provides anterograde amnesia. Even though premedication is a frequent part of the overall procedure, it should be administered purposefully, not routinely (4, 5).

Induction can be accomplished by using an intravenous or inhaled route of administrating the anesthetic agent or by combining the two. Inhaled induction is generally the method of choice for pediatric population and may also be indicated in a patient that is expected to have a difficult airway to manage because of preserved spontaneous respiratory efforts. However, this is not always the case, as inhalation anesthetics also diminish protective airway reflexes. When resorting to inhaled induction, sevoflurane is the agent of choice due to its high potency and rapidity of onset. Intravenous induction is the most common method in the adult patient. Agents most commonly used for intravenous induction are propofol, etomidate, thiopental, ketamine and a benzodiazepine-opioid combination (10). In addition to the induction agent, most patients receive an opioid analgesic, which works synergistically with the induction agent to induce anesthesia (4).

After application of the anesthetic, it is necessary to secure the airway. When possible, preoxygenation with face mask oxygen should precede all airway management interventions. Oxygen is delivered by mask for several minutes prior to anesthetic induction (2).

The airway can be managed in various ways, ranging from manually holding the patient's jaw in order to prevent the tongue from interfering with the natural breathing process to inserting a prosthetic device, such as a laryngeal mask airway or an endotracheal tube. The choice of airway technique management depends on the preoperative airway assessment, depth of anesthesia, type of surgery, etc (4).

After induction, anesthesia is maintained throughout the entire length of the procedure using intravenous agents, continuous administration of inhalation anesthetics or combining both with the dose adjusted to produce a certain anesthetic effect, while minimising the adverse effects (10). Although the choice of the maintenance method depends on various indications, such as the type of surgery, the most commonly used method is continuous administration of an inhalation anesthetic (4). Inhalation anesthetics are easily titratable, reduce the autonomic response to noxious stimuli and facilitate muscle relaxation. However, they are associated with increased incidence of postoperative nausea and vomiting, coughing and airway hyperactivity.

Some intravenous agents, such as propofol, have the advantage of reduced incidence of postoperative vomiting and nausea, coughing and laryngospasm risk compared to inhalation anesthetics (10).

Emergence is planned in accordance with the end of the surgical procedure and it represents the time following the cessation of anesthetic administration until the patient is able to respond to a verbal command. Emergence should be characterized by gradual awakening in a controlled environment. Frequently occurring problems at this stage are airway obstruction, delirium, agitation, transient aphasia, hypothermia, shivering, nausea and vomiting (2, 7). Speed of emergence from an inhalation anesthetic is proportional to alveolar ventilation and inversely proportional to the anaesthetic's blood solubility. Emergence from intravenous anesthetic agents is mostly dependent on redistribution of the drug. Premedication also influences the speed of emergence, e.g., drugs that have a long-lasting effect, such as lorazepam may prolong emergence. Ventilation assisting devices are removed at this time, if the appropriate criteria have been met. Adequate analgesic agents should be administered for continued analgesia in the postoperative period (4, 7).

The modern practice of anesthesiology relies on the use of combinations of intravenous and inhalation agents, so called balanced anesthesia. This approach is believed to increase the likelihood of a drug's desired effects and reduce the likelihood of its side effects (8). There is evidence that balanced general anesthesia uses less of each drug than if the drug were administered alone (9). In most cases, balanced general anesthesia relies on a administering an intravenous hypnotic agent, such as propofol, for induction and on an inhalation anesthetic or a hypnotic infusion for maintenance of anesthesia. Midazolam is frequently administered prior to induction to relieve anxiety. Muscle relaxants are administered to produce immobility, but administration of propofol and of inhalation anesthetics contributes to muscle relaxation as well (8).

Patients that have been anesthetized stay in the operating theatre until they have a patent airway, adequate ventilation and oxygenation and are hemodynamically stable. When these criteria have been met, the patient is transferred to the postanesthesia care unit (PACU). Upon arrival to the PACU airway patency, vital signs, oxygenation and level of consciousness are assessed. Repeated measurements of heart rate, respiratory rate and blood pressure should be made every 5 to 15 minutes until stable and every 15 minutes after that. In addition, neuromuscular function should be clinically assessed and temperature measurement should be obtained at least once. Pain assessment should be done, presence or absence of postoperative nausea and vomiting should be noted, as well as fluid input and output (2).

Discharge criteria from the PACU include: absence of respiratory depression for at least 20–30 min after the last dose of parenteral opioid, easy to arouse, full orientation, ability to maintain and protect the airway, stable vital signs (for at least 15 to 30 minutes), ability to call for help,

no evident surgical complications, control of postoperative vomiting and nausea, normothermia (2).

1.1. General anesthetics

The mechanism of action of general anesthetics Is found to be at multiple levels of the central nervous system (CNS), although it is still largely unknown. They exert their effects at various neuronal cellular locations, with the primary focus being the synapse. Acting on the presynaptic portion may alter release of neurotransmitters, while acting on the postsynaptic portion may change the frequency or amplitude of impulses that exit the synapse. Chloride and potassium channels are the primary inhibitory ion channels that facilitate anesthetics action. Ion channels activated by acetylcholine, by glutamate or by serotonin are the responsible excitatory channels. (6)

1.1.1. Inhalation anesthetics

Inhalation anesthetics can be divided into volatile and gaseous anesthetics. Volatile anesthetics have low vapour pressures and high boiling points and are liquids at room temperate (20°C) and sea-level ambient pressure. The most commonly used in clinical practice are sevoflurane, isoflurane and desflurane. Gaseous anesthetics on the other hand, have high vapour pressures and low boiling points, and are gases at room temperature and sea level ambient pressure. The two most common examples are nitrous oxide and xenon. (6)

The mechanism of action of inhalation anesthetics is not yet fully understood. On a synaptic level inhalation agents act presynaptically to alter neurotransmitter release, postsynaptically to alter neurotransmitter response, or both. Inhalation agents appear to inhibit the activity of excitatory presynaptic channels mediated by nicotinic, glutamatergic and serotonergic receptors. In addition, they enhance the inhibitory activity of post-synaptic channels mediated by γ-aminobutyric acid (GABA) and glycine receptors. At the spinal level a reduction excitatory transmission, especially at the level of the dorsal horn interneurons that are involved in pain transmission has been shown. Inhalational agents reduce cerebral blood flow and decrease cerebral glucose metabolism (2, 45).

Administration of inhalation anesthetics requires a physical delivery system that maximizes patient exposure to the anesthetic and minimizes operating theatre staff exposure. Such needs can be met by using closed-circuit devices (11). Due to their properties, volatile agents are administered using specially designed vaporisers. They are delivered through a mixture of carrier gases which are either pure oxygen or a mixture of oxygen and air or nitrous oxide (2). Gaseous agents, such as nitrous oxide, are delivered from cylinders on the anesthetic machine or as a part of the pipeline supply (12). The fresh gas leaving the anesthesia machine is mixed

with gases in the breathing circuit before being delivered to the patient via a face mask, laryngeal airway or tracheal tube (2).

To produce the anesthetic state, sufficient concentrations must be achieved in the CNS. For this to happen, effective partial pressures must be established within the alveoli. This will allow gases to equilibrate in the pulmonary vasculature and eventually with the CNS. At equilibrium the partial pressures of the gases will be equal in the alveoli, the blood and the brain.

The minimum alveolar concentration (MAC) of an inhalation anesthetic is defined as the alveolar concentration that prevents motor response in 50% of patients in response to a standardized stimulus (e.g., surgical incision) (2, 13). MAC represents brain partial pressure and allows comparisons of potency between various inhalation agents. MAC values of different anesthetics are roughly additive (2). MAC is increased (decrease in potency) by: hyperthermia, stimulants (cocaine, amphetamines), and chronic alcoholism. MAC is decreased (increase in potency) by: hypothermia, hyponatremia, opioids, barbiturates, alpha-2 blockers, calcium channel blockers, acute alcohol intoxication, pregnancy and aging (13).

Figure 1. Structure of Sevoflurane. PubChem. Sevoflurane [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Sevoflurane (177)

Figure 2. Structure of isoflurane. PubChem. Isoflurane [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Isoflurane (178)

1.1.2. Intravenous anesthetics

Intravenous anaesthetics are used for induction, maintenance of anaesthesia, sedation during monitored anesthesia and in the intensive care unit (ICU) and surgeries performed under local anaesthesia (3, 6). In modern practice, the intravenous nonopioid anesthetics are the usual method of induction of general anesthesia in adult patients. Their lipophilic properties allow for their rapid distribution into lipid rich tissues such as the brain and spinal cord, which leads to the rapid onset of action. Their action is terminated when they are redistributed to less perfused and less active tissues such as fat (10). The introduction of propofol made intravenous

anesthesia suitable for maintenance as well. However, intravenous agents do not produce only and all of the desired effects of anesthesia. Because of this, balanced anesthesia is used to minimize unwanted effects (6).

1.1.2.1. Propofol

Propofol is the most frequently used agent for induction of anesthesia. In addition to induction, propofol is often used for maintenance of anesthesia, sedation in ICU and sedation for monitored anesthesia care. Propofol binds to the γ-aminobutyric acid type A ($GABA_A$) receptor and increases the receptor's affinity for GABA. Receptor binding causes an increase in the duration of opening of the associated chloride channel leading to membrane hyperpolarization. It is an alkyl phenol with hypnotic properties. It is not water soluble and is available as an emulsion containing soybean oil, glycerol and lecithin which carries a risk of allergic reactions for susceptible patients. This type of formulation also supports the growth of bacteria which is why sterile technique and administrating the drug as soon as possible after opening is key. Propofol has a rapid onset of action and a short half-life which accounts for rapid recovery.
Propofol causes a pronounced decrease in systemic blood pressure due to a drop in systemic vascular resistance which is even more pronounced with increasing age. The hypotensive effect is increased by impairment of the normal arterial baroreceptor reflex. It is a potent respiratory depressant which usually produces apnea after an induction dose. In addition, hypoxic ventilatory drive and normal response to hypercarbia are inhibited. Propofol administration results in a decrease of cerebral blood flow and intracranial pressure. Its antipruritic and antiemetic effects are also of clinical importance (2, 6).

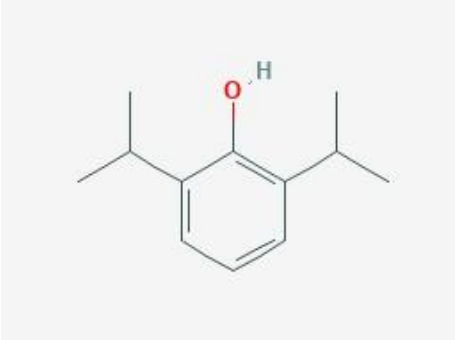

Figure 3. The structure of propofol. PubChem. Propofol [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/4943 (179)

1.1.2.2. Barbiturates

The anesthetic effect of barbiturates results from depressing the reticular activating system, which controls many vital functions, one which is consciousness. Their mechanism of action seems to be through binding to the $GABA_A$ receptor. Barbiturates prolong the openings of a chloride specific ion channel and thus enhance the action of GABA. Thiopental, thiamylal and

methohexital were frequently used intravenously for induction of general anesthesia. Today they are mostly replaced by propofol. The duration of action of lipid soluble barbiturates used in clinical practice depends on redistribution to peripheral tissues. Intravenous induction doses of barbiturates cause a decrease in systemic blood pressure due to peripheral vasodilation after which compensatory tachycardia ensues. Barbiturates are respiratory depressants, they decrease ventilatory response to hypercarbia and hypoxia. They may cause transient apnea following induction dose. Barbiturates are potent constrictors of cerebral vasculature causing a decrease in cerebral blood flow, cerebral blood volume and intracranial pressure which results in decreased cerebral oxygen consumption. Barbiturates do not produce analgesia (2, 6).

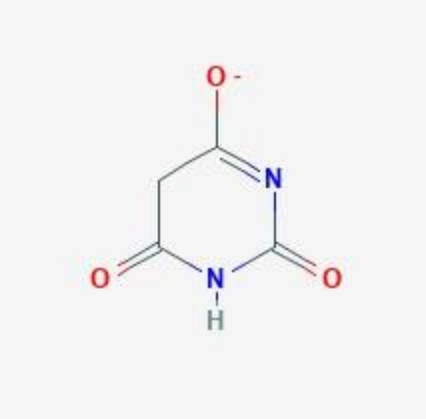

Figure 4. Structure of barbiturate. PubChem. Barbiturate [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Barbiturate (180)

1.1.2.3. Ketamine

Ketamine causes functional dissociation of the thalamus from the limbic cortex producing a state of “dissociative” anesthesia in which the patient’s eyes remain open with a slow nystagmic gaze. Even though the patient may seem conscious, he or she is not able to process or respond to sensory input. It is an N-methyl-d-aspartate (NMDA) receptor antagonist. Ketamine is used intravenously for induction of anesthesia, especially when the patient may benefit from sympathetic stimulation (hypovolemia, trauma). It can also be administered intramuscularly. Due to its lipid solubility it as a rapid onset of action. Ketamine increases arterial blood pressure, heart rate and cardiac output by centrally mediated sympathetic stimulation. Ketamine does not produce significant respiratory depression. It is thought to increase cerebral oxygen consumption, cerebral blood flow, and intracranial pressure. Additionally, it has potent analgesic properties. Ketamine displays unpleasant emergence phenomena such as hallucinations, vivid colourful dreams and out-of-body experiences (2, 6).

Figure 5. Structure of ketamine. PubChem. Ketamine [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/3821 (181)

1.1.2.4. Etomidate

Etomidate is an intravenous anesthetic with hypnotic but lack of analgesic properties. It binds to a subunit of the $GABA_A$ receptor and increases the receptor's affinity for GABA, acting to depress the reticular activating system. It is available only for intravenous administration and is mostly used for induction of general anesthesia. It has a very rapid onset of action. Etomidate has minimal cardiovascular effects and has a less pronounced effects on respiration than those of barbiturates. Etomidate is a potent cerebrovascular constrictor, causing a decrease in cerebral metabolic rate, cerebral blood flow, and intracranial pressure. Incidence of postoperative nausea and vomiting are higher than after administration of barbiturates or propofol. Etomidate causes adrenocortical suppression that lasts 4 – 8 hours after an induction dose (2, 6).

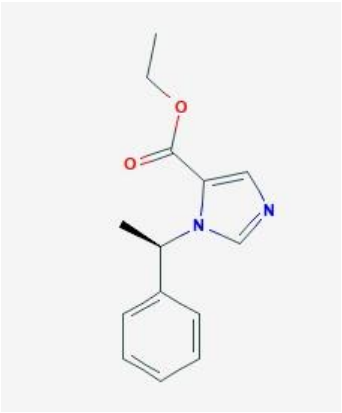

Figure 6. Stucture of etomidate. PubChem. Etomidate [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/667484 (182)

1.1.2.5. Benzodiazepines

Benzodiazepines act through binding to the $GABA_A$ receptor. Receptor binding increases the frequency of openings of the related chloride ion channel. Benzodiazepines such as midazolam, lorazepam and to a lesser extent diazepam are frequently used in the perioperative period. Their action can be terminated by administrating flumazenil, a selective benzodiazepine-receptor antagonist. They are highly lipid-soluble and enter the CNS quickly, which accounts for their rapid onset of action. Their action is terminated by redistribution to peripheral tissues. Benzodiazepines can be administered orally, intramuscularly or intravenously to provide sedation or, less frequently, for induction of general anesthesia. They are also used to suppress seizure activity. When used alone, they display minimal cardiovascular depressant effects and depress the ventilatory response to hypercarbia. Benzodiazepines decrease cerebral oxygen consumption, cerebral blood flow, and intracranial pressure, but to a lesser extent than barbiturates. They are also effective in producing antegrade amnesia and have mild muscle relaxing properties. They have no analgesic properties (2, 6).

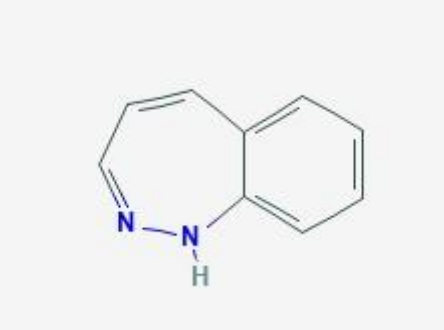

Figure 7. Structure of benzodiazepine. PubChem. Benzodiazepine [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/134664 (183)

1.1.2.6. Opioids

Opioids are a class of endogenous, naturally occurring, and synthetic compounds. They are primarily used to produce analgesia (13). Pharmacologic effects of opioids are produced through interaction with opioid receptors (10). There are four major types of opioid receptors: μ (with subtypes μ1 and μ2), κ, δ and σ and they are all G-protein coupled receptors. The effects produced through opioid receptor binding are primarily inhibitory and result in cell hyperpolarization and reduction of neuronal excitability (2, 10). The analgesic effects of opioids are primarily achieved at the brain, spinal cord, and peripheral tissues via mu1 and mu2 receptors. Opioids also cause sedation, euphoria, dysphoria, cough suppression, miosis, nausea and vomiting and sleep disturbances (decreased rapid eye movement and slow-wave sleep) (6, 13). All opioid analgesics are capable of producing significant dose dependent

respiratory depression by inhibiting respiratory mechanisms in the brainstem. Opioids also cause peristalsis reduction and constipation (2, 6).

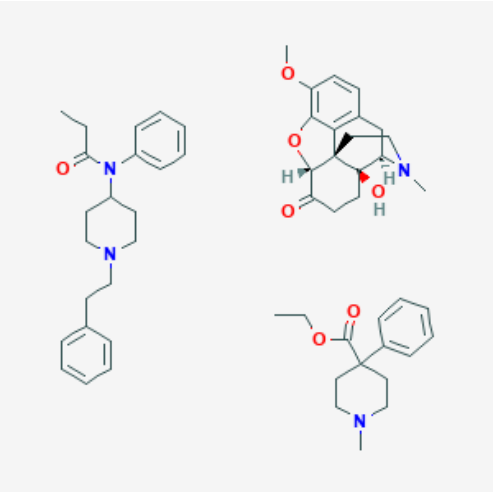

Figure 8. Structure of opioids. PubChem. Opioid [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/126961754 (184)

2. Sleep

Sleep is a recurring, reversible state of altered consciousness, reduced responsiveness to external stimuli and reduced interaction with the environment (14). It is an active state, characterized by complex regulation and metabolism alternations and is essential for both mental and physical health (15).

Sleep is not a uniform process and consists of cyclical changes of different phases of sleep: non-rapid eye movement (NREM) and rapid eye movement (REM). Around 75% of total sleep time is spent in NREM and around 25% in REM phase. NREM can be further subdivided into stages 1-3. REM phase is when dreaming occurs and it is characterized by paralysis of voluntary muscles in the entire body (except extraocular muscles). A normal sleep pattern through one night involves repeated cycling from NREM into REM and then back to NREM sleep. The first cycle lasts 70 to 100 minutes, while the following cycles last 90 to 120 minutes each. One night tends to have a total of four to five cycles.

The first stage a healthy individual enters after sleep onset is Stage 1. Sleep is shallow at this stage and the electroencephalogram (EEG) alpha rhythms become less regular and wane. This stage lasts only a couple of minutes. It is followed by Stage 2, which is slightly deeper and lasts on average 5 to 15 minutes. At this stage the EEG may display the sleep spindle, an occasional 8–14 Hz oscillation or a high-amplitude sharp wave called the K complex. Eye movements are almost completely absent. Stage 2 lasts approximately 10 to 25 minutes in the initial cycle. At Stage 3 the EEG displays to high-voltage, slow-wave frequency called delta

waves. The eye and body movements are almost non-existent. Stage 3 of the first sleep cycle lasts 20 to 40 minutes. It is commonly referred to as “Slow-wave sleep” (SWS) (107). After this, sleep regresses back to stage 2 followed by a short period of REM sleep. During REM sleep the EEG displays a fast, beta and gamma rhythms and rapid eye movements can be seen. As sleep progresses through the night a reduction in the duration of NREM sleep occurs (mostly in stage 3) while REM periods are increased. After every REM period there is an obligatory refractory NREM period lasting at least 30 minutes before another REM period can happen (14, 16).

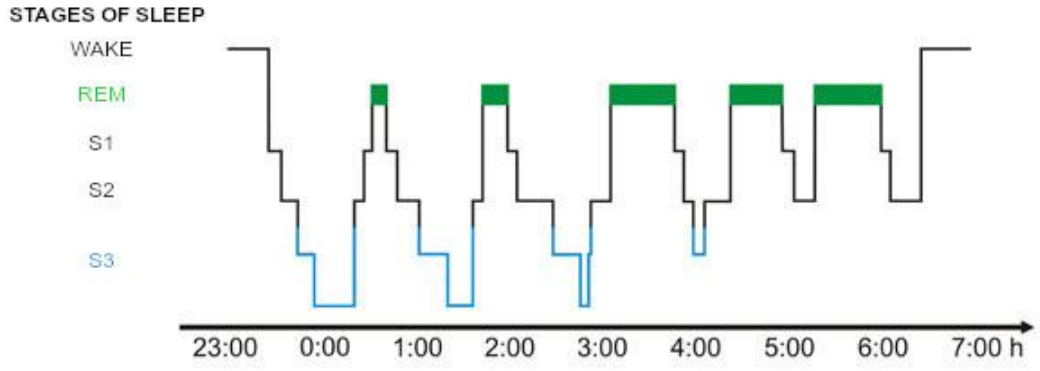

Figure 9. Stages of sleep.

Sleep onset is generated within the ventrolateral preoptic nucleus (VLPO), a part of the anterior hypothalamus. The VLPO acts via inhibitory neurotransmitters (GABA and galanin) to suppress the neuronal activities of brain regions that comprise the ascending arousal system. The ascending arousal system maintains wakefulness and there are several neurotransmitters and associated neuronal regions implicated in the process: Norepinephrine (locus ceruleus), histamine (tuberomammillary nucleus), serotonin (middle raphe nuclei), dopamine (ventral periaqueductal grey matter), acetylcholine (pedunculopontine tegmentum and laterodorsal tegmentum of the pons) and orexin (perifornical area) (14, 19).

NREM sleep is maintained by hyperpolarizing GABA neurons in the reticular activating system of the thalamus and in the cortex and their rhythmic connection. GABAergic neuronal hyperpolarization and oscillating neuronal interactions between the thalamus and the cortex are seen as distinct EEG patterns seen in various stages of NREM sleep.

REM sleep is generated in the mesencephalic and pontine cholinergic neurons by “REM-on neurons”. The pedunculopontine tegmental nucleus and the lateral dorsal tegmental neurons trigger cortical desynchrony in the thalamus through acetylcholine release. Cortical desynchrony and “sawtooth waves” are hallmarks of REM sleep. The “REM-off” neurons of the locus ceruleus and raphe nuclei inhibit the REM-on neurons via norepinephrine, serotonin, and histamine. This results in cessation of REM sleep (14, 20).

Sleep is regulated by complex mechanisms, the core of which is interplay between the homeostatic factors (process S) and circadian rhythm (process C). The concept was first introduced in 1982 by Borbély and its core idea is still widely accepted today (17, 18). Together, they control sleep duration, quality, tendency to sleep and wakefulness quality.

The proposed model of function of factor S is progressive accumulation of chemicals that promote sleep during time of wakefulness. The most investigated among many proposed chemicals is adenosine. Extracellular adenosine levels in the brain increase during prolonged wakefulness and sleep deprivation and decrease during sleep. Adenosine antagonists (caffeine, theophylline) increase wakefulness, while adenosine agonists increase sleep (14, 23).

Circadian rhythm is primarily a biological clock, meaning its periodic 24-hour rhythmicity continues as more or less unchanged regardless of external factors such as cycles of light and dark. However, shifting and synchronization can occur under the influence of external factors. These factors can be natural, such as light and dark or temperature changes or artificial, such as pharmaceutical agents (14, 96, 97). The circadian clocks are heavily influenced by environmental time cues, known as zeitgebers (German for “time givers”). For mammals, light is the most potent zeitgeber. In their presence the circadian rhythm becomes entrained to the day-night rhythm and maintains a 24-hour cycle. In state of complete deprivation of zeitgebers, mammals tend to maintain an approximately 24-hour rhythm of activity. This is called a free-run rhythm.

The suprachiasmatic nucleus (SCN), a pair of neuronal clusters in the anterior hypothalamus, is considered the master circadian clock responsible for synchronization of peripheral circadian clocks found in most peripheral tissues (14, 21, 22).

The molecular components of the circadian clock are the proteins BMAL1 (brain and muscle ARNT-like 1), CLOCK (circadian locomotor output kaput), PERIOD (PER1, PER2 and PER3) and CRYPTOCHROME (CRY1 and CRY2). BMAL1 and CLOCK form a dimer to regulate gene transcription (99). The BMAL1:CLOCK dimer promotes transcription of *per* and *cry* and 98auto-inhibits *bmal1* expression. PER and CRY form a dimer as well and it acts as an inhibitor of BMAL1:CLOCK. The oscillation of BMAL1 that occurs is in antiphase with oscillations of PER and CRY and these oscillations occur in a self-dependent cycle (98, 100, 101). In a free-run rhythm, one complete oscillation of the PER:CRY/BMAL1:CLOCK cycle is completed in approximately 24 hours. Exposure to the day/night cycle sets the duration of one complete oscillation of the PER:CRY/BMAL1:CLOCK cycle to equal the earth's 24 h day/night cycle (98). Light causes activation of the SCN neurons via the retinohypothalamic tract through specialised retinal ganglion cells which containing the photopigment melanopsin (14, 102). The retinohypothalamic tract innervates a group of neurons of the ventral portion of the SCN. When light is detected by the retinal ganglion cells, this input is conveyed through the

retinohypothalamic tract to the SCN and causes activation of the NMDA receptors of the SCN neurons (14). NMDA receptor activation triggers an intracellular signalling cascade which eventually leads to transcription of *per* (103). The SCN neurons innervated by the retinohypothalamic tract synchronize with the rest of the SCN neurons via GABA signalling. (104)

PER and CRY protein levels are highest during periods of light, while BMAL1 and CLOCK protein levels are highest during the periods of darkness (98). In addition to enabling SCN synchronization, GABA plays a vital role in re-setting the clock in response to changes in the light/dark cycle (98, 105). If exposure to light during the normal dark period triggers an increase in activation of GABA receptors in SCN neurons (105, 106).

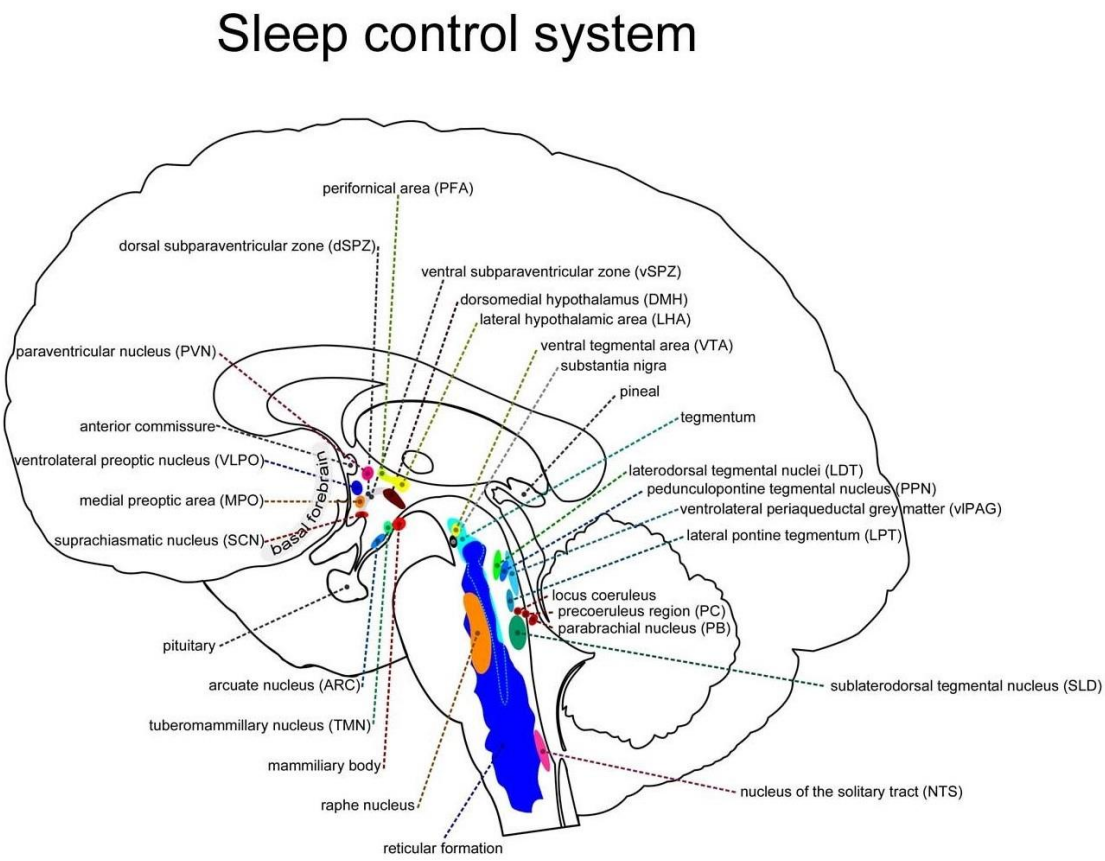

Figure 10. Sleep control system [Internet]. Supermemo.guru. [cited 2021 Apr 16]. Available from: https://supermemo.guru/wiki/File:Sleep_control_system.jpg (185)

2.1. Hormones and their link to the circadian system and sleep

2.1.1. Melatonin

Melatonin demonstrates a strong circadian rhythmicity. Melatonin production is regulated by the SCN, through the autonomic nervous system (23). Its levels are highest towards the end of the biological day, peaking between two and four a.m. and gradually declining during the second half of the biological night (24, 25, 28). Melatonin plays an important role in sleep regulation. Administration of exogenous melatonin when not endogenously present during daytime, causes fatigue, a sense of sleepiness and a decrease in sleep latency (27). Ageing, drugs (e.g., β-blockers) and certain diseases (e.g., Alzheimer's disease, primary degeneration of the autonomic nervous system) disrupt endogenous melatonin production and cause sleep disturbances (28). Melatonin is considered to be a possible treatment option in some primary insomnia, delayed sleep phase syndrome, non-24 h sleep-wake disorder as well as in people who are blind (29-32).

2.1.2. Cortisol

Cortisol displays a marked circadian rhythmicity. Cortisol levels gradually rise during the second half of the biological night and reach their peak during biological morning, approximately 30 minutes after awakening. After reaching its peak in the morning, cortisol levels gradually decline (26, 33). Cortisol's rhythmic secretion is regulated by the SCN via neuronal and hormonal pathways. Behavioural sleep patterns display an inhibitory effect on cortisol secretion demonstrating that sleep occurring at any time of habitual wakefulness is associated with decreased levels of cortisol (34-37). Exogenous cortisol administration has been shown to affect sleep architecture, however, the mechanism of cortisol's influence on sleep is not yet fully understood (23, 38, 39).

2.1.3. Growth hormone

Association of growth hormone secretion with circadian rhythm has been observed. Growth hormone levels increase during sleep, most significantly after sleep onset. The increase occurs irrespective of the time of day or night that sleep takes place (40-43). If nocturnal sleep is interrupted, a surge in growth hormone occurs shortly after sleep is continued (44).

2.1.4. Thyroid stimulating hormone

Thyroid stimulating hormone displays a circadian rhythm. Its level reaches a peak in the middle of the biological night and drops to the lowest point in the biological afternoon (46). Sleep acts

on thyroid stimulating hormone in an inhibitory fashion and its values are especially inhibited by SWS (47, 48).

2.1.5. Glucose and insulin

Glucose and insulin have been shown to correlate with the circadian rhythm (49, 50). Highest levels are observed in the transition between biological day and night (51). In addition, synaptic projections from the SCN to the liver and pancreas have been discovered, demonstrating further connections of glucose and insulin to the circadian clock (52, 53).

2.1.6. Prolactin

Circadian rhythm of prolactin levels is present in men. The levels are at their peak during the end of the biological afternoon, evening and night. Prolactin levels in women also display circadian rhythmicity but are dependent on the menstrual cycle as well (54).
Findings also suggest an increase in prolactin level after sleep onset and continuous elevation irrespective of the time of day at which sleep commences (55-57). Various and conflicting results have been published about the link between prolactin secretion and distinct stages of sleep (23).

In addition to the above mentioned: progesterone, neuropeptide γ and growth hormone releasing hormone can enhance sleep, while adrenalin and cortisol can inhibit sleep (60).

2.2. Sleep function

The function of sleep is to this day not fully understood. There are numerous theories about the primary function of sleep.
The restorative theory focuses on the importance of inactivity that occurs during sleep. It is proposed that inactivity makes restoration of resources depleted during wakefulness possible and allows energy conservation. As already mentioned, levels of anabolic hormones such as growth hormone and prolactin are increased during sleep. In addition, research has shown that decreased sleep quality and sleep deprivation may negatively affect wound healing (58, 59).
Another component of the restorative theory is specific to the brain. During wakefulness brain accumulates byproducts of activity and due to the constant high-level functioning is unable to clear them away. The main byproduct is considered to be adenosine. During the period of inactivity that happens during sleep, especially during NREM sleep, the brain is able to clear away the excess adenosine along with the other accumulated substances (60, 61). It has also been demonstrated that the brain is able to restore compounds such as glycogen during this state of lower activity (62).

The brain plasticity theory is among the most recent theories that has emerged from findings that sleep is linked to structural and organisational changes in the brain. The processes underlying this theory are not yet entirely understood (60). One of the proposed mechanisms is that sleep helps recover and stabilize synapses involved in learning and memory. This is achieved by maintaining individual synapses and integrating new synaptic patterns produced through obtaining new experiences (63). This theory may explain the role of sleep in memory consolidation as well (60).

The inactivity theory proposes sleep is a behavioural adaptation termed “adaptive non-responding” (64). For animals whose primary sensory input comes from the eyes and whose eyesight is adapted to achieve maximal efficiency during daylight, night time presents a period of increased vulnerability. Activity during such a time makes them more likely to attract attention of a predator or to succumb to an accident. Another reason for night time inactivity is decreased food availability (60).

The energy conservation theory is based on findings of decreased body temperature and caloric demand during sleep. This need may not be as evident in modern societies and many scientists in fact link it to the inactivity theory (60, 61).

2.3. Sleep deprivation

Sleep deprivation can be defined as either quantitative or qualitative or a combination of the two. Quantitative sleep deprivation is a result of insufficient nocturnal sleep duration. Qualitative sleep deprivation occurs due to disordered sleep architecture or an increased number of arousals and awakenings in a night’s sleep (65).

Sleep deprivation has a marked impact on an individual’s mood and functioning, causing increased sleep latency, excessive sleepiness and impaired concentration and attention (65, 73-75). Sleep deprivation has also been implicated in significant alteration of work performance. Task management and efficiency are significantly affected by both one night and longer periods of sleep restriction (76, 77). Additional negative behavioural effects include aggression, deterioration in interpersonal relationships and an increase subjective perception of symptoms such as anxiety, depression, mania (78, 79).

Lack of sleep has been linked with negative effects on the immune system, demonstrating an increased susceptibility to infections (65-68). Sleep deprivation greatly influences the host defence mechanisms. Literature suggests leukocyte migration shows circadian rhythmicity and sleep has been shown to affect the leukocyte circulating numbers and migration (66). Interleukin-6 plasma levels increase after an individual has been sleep deprived for more than one night (69-71). Both animal and humas studies have shown that prolonged sleep deprivation is linked to a state of chronic systemic low-grade inflammation, making it a potential risk factor for diseases such as atherosclerosis, diabetes and neurodegeneration (65, 72).

Inadequate sleep plays a major role in metabolism homeostasis. A connection between inadequate sleep and obesity has been established (82). Increased ghrelin and decreased leptin concentrations lead to increased hunger and appetite in sleep deprived individuals (80). Increased levels of T3, T4 and TSH concentrations, as well as an increased rate of ACTH secretion and plasma cortisol level were measured after 24-hour sleep deprivation. In contrast, measured plasma aldosterone concentration and renin activity were decreased (83-85).

2.4. Alcohol and sedatives in relation to sleep

Sleep is a major factor in the individual's quality of life. Sleep disorders are a common problem in the general population and despite their importance and influence on everyday living a large proportion of them remains undiagnosed (86).

Alcohol (referring to ethanol) is one of the most frequently used "over the counter" drugs to combat sleep disturbances. The reason for this is its potent sleep-promoting and relaxant properties. In non-alcoholics, alcohol tends to reduce sleep onset latency and enhance the quality and quantity of NREM sleep. This however occurs only during the first half of the night, while sleep during the second half is markedly disrupted (87-89). Specifically, increased wake periods or light sleep were observed in the second half of total sleep time. This was particularly evident in higher doses of alcohol (89, 90). Studies also demonstrated a suppression of REM sleep during the first half of total sleep time (89). A study that used actigraphy to measure the effects of alcohol on sleep reported a decrease in total sleep time regardless of the dose of alcohol consumed, as well as higher subjective levels of fatigue the morning after alcohol consumption (91).

Benzodiazepines, as already mentioned, are sedatives that act through binding to the $GABA_A$ receptor and enhancing the inhibitory effect of GABA. They are recommended as treatment of insomnia (92, 93). Benzodiazepines have been associated with a certain degree of decrease in sleep latency and an increase in total sleep time. However, benzodiazepines alter sleep architecture by suppressing REM sleep and increasing stage 2 sleep which may decrease the overall restorative effect of sleep (94, 95).

3. General anesthesia and sleep

Historically, general anaesthesia and sleep have been linked by their behavioural similarity. Research has proved that they share much more than just appearance (108).

General anesthesia and sleep display similarities in EEG patterns. The majority of general anesthetics produce sleep spindles and delta waves. The exceptions to this are ketamine and nitrous oxide. The spindles and delta waves seen on the EEG are characteristics of EEG recordings found during NREM sleep stages 2 and 3, respectively (108-110).

Functional brain imaging has displayed similarities as well. Both sleep and general anesthesia display depressed activity in the thalamus, brainstem, basal forebrain, basal ganglia and certain regions of the frontal and parietal cortices (108, 111-113).

The EEG findings combined with functional brain imaging results suggest a common neuronal pathway involved in both sleep and general anesthesia (108).

Additional links between general anesthesia and sleep, such as the one through the orexin system, have been established as well. The orexin system is involved in sleep regulation. Administration of orexin agonists causes a decrease in the depth of anesthesia. Orexin receptor-1 antagonist administration, on the other hand increases the duration of anesthesia (114-116).

Despite the listed similarities between sleep and general anesthesia, most animal studies have provided evidence that sleep and anesthesia are in fact significantly different in terms of actual rest and recovery.

3.1. General anesthesia and the circadian rhythm

It is difficult to separate general anesthesia from surgery in humans, as surgery is the most common setting for general anesthesia utilization. The postoperative period has been shown to disrupt circadian rhythms, but there are relatively few human studies that examine the influence of general anesthesia on circadian rhythms separated from surgery (117-120). This lack of studies in humans is why animal studies have proven valuable in expanding knowledge related to these topics.

Animal studies have shown that general anesthetics have a significant influence of circadian rhythms, although the precise mechanisms involved are still unknown (98).

Ludin et al. showed that isoflurane causes a time dependent behavioural phase shift as well as phase shifts in PER2::LUC expression in mice (121). Another study performed on honey bee colonies (Apis mellifera) demonstrated that isoflurane administration during subjective day causes a phase delay. However, when isoflurane was administered during subjective night, no

phase shift was documented. The same study also showed that when bee colonies were exposed to bright light in addition to isoflurane during subjective day no phase shift was evident. This finding might have potential therapeutic benefits (122). Li et al. demonstrated that isoflurane administration in Drosophila melanogaster resulted in behavioural and gene expression circadian clock phase shifts. Isoflurane administration during the subjective morning resulted in Phase advances in behaviour while administration during night-time resulted in behavioural phase delays. The same pattern was observed with gene expression, but preceded the behavioural shift by four hours (123). Desflurane anesthesia in mice resulted in rest/activity phase shift, with the magnitude of phase shift being dependent on the time of day at which the anesthetic was administered. Clock gene expression showed alterations in the same manner (124). Administration of sevoflurane anesthesia in mice which were exposed to light during subjective night exhibited repressive effects on mPER2 expression. In contrast, mice which were exposed to light but not to sevoflurane exhibited a marked increase in mPer2 as expected. Behavioural analysis of the anesthesized mice showed backward phase shift in the circadian rhythm (125). Challet et al. demonstrated that propofol administration at the daily rest/activity transition point results in phase advance. No significant phase alterations occurred when anesthesia was administered at other times of the day (126).

Although scarce, the few available human studies seem to support the results of animal studies in terms of general anesthesia having a marked influence on the circadian clock. Dispersyn et al. observed that propofol anesthesia impacts the circadian rhythm in humans exposed to real-life conditions. The study demonstrates a transient, but significant increase in diurnal rest periods as a consequence of daily rest-activity rhythm desynchronization following propofol anaesthesia administered for colonoscopy (127).

Song et al. demonstrated that operations performed in the evening were linked with more pronounced postoperative sleep disturbances than operations performed in the morning. In addition, patients undergoing evening operations required lager doses of propofol than patients operated on in the morning which could partly explain the more pronounced postoperative sleep disturbances. These findings correlate with the previously mentioned results of animal studies implicating a close link between effects of general anesthetics and the time of their administration (128).

It is evident that the extent and type of disruption depend on the anesthetic used, the timing of administration and the presence of other stimuli affecting the clock (121). It is hypothesized that at least a part of the answer lies in the fact that general anesthetics affect neurotransmitters (such as GABA and NMDA) involved in regulation of the circadian system. Poulsen et al. proposed that anesthetics that act as NMDA receptor antagonists inhibit the light entrainment of the circadian clock, while agents acting on GABA receptors cause phase shifts in the circadian clock by sustained receptor activation (98). While this hypothesis might be part

of the answer the exact mechanism is likely to be more complex and requires further research to be determined.

3.2. General anesthesia and postoperative sleep disturbances

The postoperative period is frequently marked by sleep disturbances of various severity. Quality of sleep in the postoperative period is known to be affected by numerous factors such as surgical trauma, preoperative comorbidities, environmental factors in the ICU (noise, healthcare staff, lights) and use of general anesthesia (129, 130).

General anesthesia represents a likely factor in contributing to postoperative sleep disturbances due to the fact that it acts on the same parts of the CNS that are involved in sleep regulation. The hypothalamus, which contains the VLPO, seems to be the target of general anesthetic action (129). As already mentioned, the VLPO acts via GABA to inhibit the arousal system and is therefore considered crucial in sleep promotion. General anesthetics, such as propofol, act on GABA receptors and enhance the activity of GABA in the VLPO. Broadly speaking, general anesthesia exerts its effects by activating sleep-promoting nuclei in the brain and inhibit wake-promoting nuclei (131, 132).

Animal studies are significant contributors to the current knowledge on the effect of general anesthesia on postoperative sleep. They enable studying the effects of general anesthesia on sleep in the postanesthetic period without the influence of factors brought about by surgery. Evaluating how various general anesthetics compare to natural sleep and thus influence sleep architecture might be the key to understanding their overall mechanism of action and better understanding of the potential side effects.

Tung et al. studied the effect of propofol on sleep deprived rats. The study showed that following 24-hour sleep deprivation the rats anesthetized with propofol for six hours displayed recovery from sleep deprivation to a similar extent as rats that were allowed ad libitum sleep for six hours following deprivation. Based on these results the authors concluded that propofol satisfies the need for both NREM and REM sleep (133). Attempting to replicate these results in another species, Gardner et al. performed a study on sleep deprived Drosophila melanogaster to determine whether propofol satisfies the need for homeostatic sleep. In contrast to the previously mentioned study performed on rodents the results showed that prior sleep debt did not resolve during propofol anesthesia. Instead, a delay in recovery sleep until after emergence from anesthesia occurred and a net increase in sleep 24 hours after propofol treatment was recorded (134).

Pal et al. investigated the effects of sevoflurane on sleep homeostasis. Their study was conducted on three groups of male rats that were sleep deprived for 12 hours. In the first group sleep deprivation was followed by 36 hours of ad libitum sleep. In the second group, sleep

deprivation was followed by 24 hours ad libitum sleep, while the third was exposed to sevoflurane for six hours followed by 18 hours of ad libitum sleep. It was concluded that the expected increase in NREM sleep did not occur in the sevoflurane group, suggesting that sevoflurane affects NREM and REM sleep differently and only satisfies the homeostatic need for NREM sleep (135). Additionally, Mashour et al. concluded that isoflurane anesthesia does not satisfy the need for REM sleep by studying the effect of the anesthetic on rats deprived of REM sleep (136).

Pick et al. conducted a study on mice to examine the various anesthetics on sleep architecture following six-hour exposure. The study demonstrates that isoflurane and sevoflurane fulfil the homeostatic need for NREM sleep, but halothane does not. All three anesthetics caused a significant rebound in REM sleep, implicating a debt in REM sleep. In addition, the authors observed a shorter latency to REM sleep onset, which supports the findings of REM sleep debt (137).

Takashi et al. conducted a study on rabbits administering ketamine and isoflurane separately to determine each agent's influence on postoperative sleep. The results displayed a decrease in NREM sleep following isoflurane anesthesia. In contrast, an increase in NREM sleep was observed following ketamine anesthesia suggesting that ketamine might exhibit less of an influence on postoperative sleep (138).

The influence of general anesthesia on postoperative sleep quality is far more complex to asses than in animal models. Additionally, human studies are at the present moment still scarce, as this subject has been brought to light only in the past few decades.

After observing three groups of patients, each group anesthetized with different agents to produce a state of general anesthesia, and comparing them to healthy volunteers sleeping in the same conditions Lehmkuhl et al. concluded that any type of anesthesia causes sleep disturbances (143).

One of the few studies performed to assess the sleep quality following general anesthesia without the contribution of surgical factors is the one performed by Lei et al. The authors studied the effects of sedatives on the quality of sleep after upper gastrointestinal endoscopy. The Pittsburgh Sleep Quality Index (PSQI) of patients that chose to undergo upper gastrointestinal endoscopy while sedated with sufentanil and propofol was compared to the PSQI of patients that chose to undergo the procedure without sedation. The PSQI score for both groups was measured before the procedure, one week after and one month after the procedure. The PSQI scores indicated sleep quality impairment in the sedative group for one week after the procedure. Based on the obtained PSQI scores, the authors concluded that propofol and sufentanil may affect sleep quality independently of surgery related factors (139).

Tan et al. performed a study on patients scheduled for thyroidectomy to assess the influence of maintenance agent choice on postoperative sleep quality. The included patients were

divided into two groups based on the maintenance agents used. In the first group anesthesia was maintained with sevoflurane, while in the second propofol was used for maintenance. In both groups anesthesia was induced with midazolam, fentanyl, propofol and cisatracurium and no opioids were used for postoperative pain management. Based on the bispectral index measurements performed on the first postoperative night, the authors concluded that the propofol group displayed less disturbed sleep patterns than the sevoflurane group (149).

Ayuse et al. examined the effects general anesthesia exerted on postoperative sleep in dentally disabled patients. The sleep cycles of patients included in the study were measured using a sleep monitoring mat starting five days preoperatively until five days after being discharged from the hospital. Ether mask induction with oxygen, sevoflurane or rapid intravenous induction was performed in all patients. Anesthesia was maintained with sevoflurane and remifentanil. Postoperative analgesia was accomplished using paracetamol. The results showed a reduced percentage of deep sleep (stage 3) on the day of general anesthesia and the day following general anesthesia. REM sleep was found to be markedly reduced on the day of general anesthesia. An increase in the percentage of light sleep and increased duration of sleep cycles was also observed on the day following general anesthesia (176).

Opioids are frequent components of multimodal general anesthesia and are commonly used in postoperative pain management (140). Studies evaluating opioid use independently of general anesthesia have shown that opioids disrupt sleep architecture. Decreased percentage of SWS and REM sleep, increased percentage of NREM sleep stage 2 and more frequent awakenings during the night (141, 142).

Knill et al. observed alterations in sleep architecture in patients following abdominal surgery under general anesthesia. Anesthesia was Induced with thiopental, maintained with isoflurane, nitrous oxide, fentanyl and pancuronium. Postoperative analgesia was accomplished using morphine. The focus of the study was REM sleep alterations. The authors observed diminished REM sleep during the first postoperative night and the subsequent increase in REM sleep during the following nights. Frequent awakenings and marked reductions in SWS were also observed. The authors concluded that these disruptions are far more likely to be the result of opioid administration and pain than general anesthesia (144).

Remifentanil, a highly potent, short-acting synthetic opioid has been implicated as a causative agent of sleep disturbances following its administration (145-147).

A study on patients undergoing corrective surgery for idiopathic scoliosis was done to assess the influence of remifentanil on postoperative sleep quality. The patients were divided into 3 groups, according to the type of surgery and medications used: posterior instrumentation including a wake-up test with remifentanil administration, anterior instrumentation without wake-up test administering sufentanil, and posterior instrumentation including a wake-up test

with sufentanil administration. PSQI scores were used to assess the sleep quality following surgery and compared to the scores noted before surgery. The patients were followed up for one 1 year postoperatively. The patients in the remifentanil group showed decreased quality of sleep for up to six months following the surgery (145). Steinmetz et al. investigated the effects of remifenanil on sleep quality in infants. The authors compared sleep quality assessments made by the infants' parents between two groups of infants following cleft-gum-palate surgery. Infants were randomly assigned to receive either a combination of propofol and remifentanil or a combination of sevoflurane and fentanyl anesthesia. In both groups, induction was performed by sevoflurane administration and postoperative analgesia was accomplished with paracetamol administration. Additionally, morphine was used when required. The propofol-remifentanil group showed more profound sleep disturbances upon hospital discharge, as reported by the parents (146). Attempting to examine the long-term effects of remifentanil on sleep, Wenk et al. compared PSQI scores of patients scheduled for elective surgery. The patients were randomly assigned into two groups, one group received remifentanil-based aesthesia, while the other one received fentanyl anesthesia. Anesthesia in the remifentanil group was induced by administering propofol and remifentanil and maintained with sevoflurane, oxygen and a continuous remifentanil infusion. The patients also received a bolus of fentanyl prior to discontinuing the remifentanil infusion. In the fentanyl group, anesthesia was induced with propofol and fentanyl and maintained with sevoflurane and oxygen. Postoperative pain was managed using acetaminophen and fentanyl in both groups. Patients were followed up at 3 months and 6 months after surgery. A subgroup of patients, who were termed good sleepers based on their preoperative PSQI scores, displayed PSQI scores at 3 months which indicated disturbed sleep patterns. The values returned to baseline at the 6 months follow up (147).

Rosenberg-Adamsen et al. conducted a study aiming to investigate postoperative sleep disturbances in patients undergoing laparoscopic cholecystectomy without administration of opioids in the postoperative period. Thiopental, isoflurane, fentanyl (low-dose), midazolam, suxamethonium, atracurium and nitrous oxide in oxygen were used for induction and maintenance of anesthesia. Postoperative pain was managed with ibuprofen. The patients were observed during the first preoperative and first postoperative night. Based on the EEG recordings, the authors found that patients displayed a reduction in SWS, increased stage 2 sleep and no significant alterations in REM sleep. Based on these findings the authors concluded that opioids, magnitude of surgery or both might be significant contributors to frequently observed decreases in postoperative sleep quality (148).

3.3. Impact of postoperative sleep disturbances

As already indicated, sleep deprivation has a marked influence on overall health and functioning. Sleep deprivation is shown to play a role in normal functioning of the immune system, behaviour and mood and is a potential risk factor for development of diseases such as atherosclerosis, neurodegenerative diseases and diabetes (65-68, 72-79).

In the postoperative setting sleep disturbances are presumed to be a risk factor for dimished speed and quality of recovery (150). One study has even linked the severity of postoperative sleep disturbance to the length of stay in hospital (151). Sleep disturbances are also considered to be a risk factor for developing postoperative delirium. Individuals of older age and patients who have experienced sleep disturbances prior to surgery are considered particularly susceptible (152, 153). Increased risk of adverse cardiac events has also been linked to postoperative sleep disturbances. A study following a large number of patients after percutaneous coronary intervention showed that patients who experienced disordered sleep patterns were at increased risk of further cardiovascular complications and mortality when compared to the patients that underwent the same procedure but slept normally afterwards (154). Sleep deprivation is associated with activation of the sympathetic adrenergic system which causes increased levels of blood pressure and might contribute to development of atherosclerosis (155). Pain, an important risk factor for occurrence of sleep disturbance, is also worsened by disturbed sleep (156).

4. Improving postoperative sleep

4.1. Pharmacologic methods

4.1.1. Dexmedetomidine

Dexmedetomidine is a new generation highly selective α2-adrenergic receptor agonist. It is a sedative agent with analgesic and sympatholytic properties. It is frequently used as a component of premedication, intraoperatively and as a sedative agent in the ICU (157).

Recently dexmedetomidine has been investigated as a potential agent for improving postoperative sleep.

Shi et al. investigated the intraoperative use of dexmedetomidine in breast cancer patients undergoing radical mastectomy as a method of improving postoperative sleep and recovery. Patients were divided into two groups, based on whether they received intravenous dexmedetomidine or Ringer solution prior to induction or not. Total sleep time, 9-question fatigue severity and a global 40-item quality of recovery questionnaire scores were utilized to aid the assessment. During the first postoperative night, the dexmedetomidine group had

increased total sleep time, decreased occurrence of postoperative vomiting and nausea in comparison to the group that didn't receive dexmedetomidine. Patients in the dexmedetomidine group had a lower fatigue severity score and a lower global 40-item quality of recovery questionnaire scores when compared to the control group (158). A study by Duan et al. investigated the impact of intraoperative dexmedetomidine use on postoperative sleep in non-cardiac major surgery. A decrease in postoperative sleep disturbance on the day of surgery was observed in patients that received dexmedetomidine, based on the subjective evaluation performed by the patients. Administration of low-doses of dexmedetomidine appeared to provide the greatest benefit (159). Song et al. investigated the effect of dexmedetomidine on postoperative sleep in relation to whether the agent was administered at daytime or nighttime. All patients included were scheduled for elective laparoscopic abdominal surgery. The patients' sleep was recorded using a Portable Sleep Monitor on the night prior to surgery and two nights following the surgery. Both the nighttime and the daytime group experienced sleep disturbances in a sense of decreased sleep efficiency, increased unstable sleep time and decreased time spent in REM sleep. However, the disturbances were less pronounced in the daytime group and the authors concluded that dexmedetomidine improved postoperative sleep to a greater extent when administered during daytime (160). Postoperative use of dexmedetomidine has proven itself beneficial in improving postoperative sleep as well. Chen et al. studied postoperative sleep quality in patients undergoing abdominal hysterectomy. The patients were divided into two groups based on the components of patient controlled analgesia. One group received sufentanil only, while the other received a combination of sufentanil and dexmedetomidine. Polysomnography was performed on the night before surgery and two postoperative nights. The results showed sleep disturbances in both groups. In all patients a decreased percentage of REM and Stage 3 sleep was evident. However, patients that received dexmedetomidine postoperatively showed increased percentages of stage 2 sleep, decreased percentages of stage 1 sleep, as well as improved sleep efficiency (161).

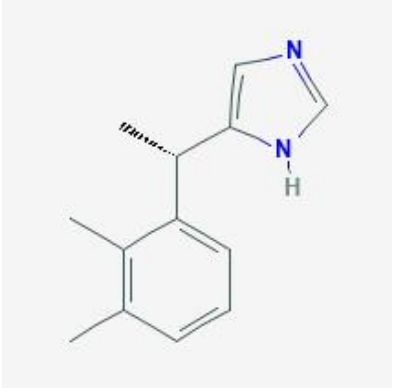

Figure 11. Structure of dexmedetomidine. PubChem. Dexmedetomidine [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Dexmedetomidine (186)

4.1.2. Zolpidem

Zolpidem is a nonbenzodiazepine sedative and hypnotic drug. It acts through binding of the $GABA_A$ receptors and increases the inhibitory effects of GABA which is responsible for its sedative effects. In addition to its sedative and hypnotic properties, it also exhibits anxiolytic, anticonvulsant and mild myorelaxant effects. It is primarily used for short-term treatment of transient insomnia and has been shown to enhance sleep quality in patients with chronic insomnia (162).

Shakya et al. performed a study on patients undergoing total hip arthroplasty. The patients were randomized into two groups and received either zolpidem or placebo two days preoperatively and five days postoperatively. Sleep quality was assessed using Epworth Sleepiness Score and PSQI. The group of patients that received zolpidem showed improved sleep quality in comparison to the placebo group. The study also demonstrated that perioperative zolpidem administration helped reduce anxiety and depression and relieve pain during the perioperative period (163).

A study by Krenk et al. showed no objective sleep improvement in patients that received zolpidem on the first postoperative night when using polysomnographic measuring. However, the patients reported subjective improvements in quality of sleep and feeling of fatigue (164).

Figure 12. Strucuture of zolpidem. PubChem. Zolpidem [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Zolpidem (187)

4.1.3. Melatonin

Endogenous melatonin, a hormone secreted by the pineal gland, is involved in the regulation of the circadian rhythm. The secretion of melatonin is promoted by darkness and inhibited by exposure to light (165). Exogenous melatonin appears to be useful in treatment of various sleeping disorders in humans (166).

A study by Borazan et al. showed that preoperative melatonin administration on the night before surgery and 1 hour prior to surgery results in markedly improved sleep quality when

compared to patients that received placebo (167). Gögenur et al. studied the effects of postoperative melatonin administration on sleep quality. Patients that underwent laparoscopic cholecystectomy were divided into two groups and received either melatonin or placebo on the 3 nights following surgery. Patient sleep quality was assessed by questionnaire and sleep diary. The results displayed a significant decrease in subjective sleep latency on the first postoperative night in the melatonin group (168). Another study in which melatonin was also administered to patients after laparoscopic cholecystectomy for three days supported the previously mentioned results and also found that subjective sleep latency was decreased on the first postoperative night. Additionally, the patients reported increased total sleep time on the first and second postoperative night, as well as decreased day time naps and frequency and duration of awakenings during the night (169). Madsen et al. examined the effects of both preoperative and postoperative melatonin administration in patients scheduled for breast cancer surgery. The patients were randomized into two groups, one received melatonin and the other received placebo for three nights preoperatively and up to one week postoperatively. The authors attempted to measure the objective effects of melatonin administration by actigraphy. They found that patients in the melatonin group displayed an increase in sleep efficiency and reduced wake after sleep onset during the first two postoperative weeks, but no other effects on objective sleep outcomes were discovered. Subjective sleep quality improvements were also not displayed (170).

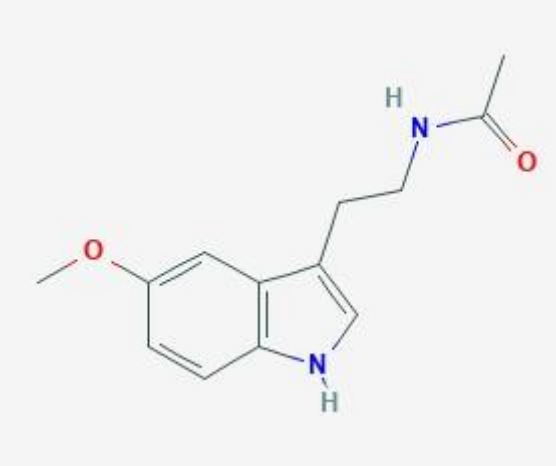

Figure 13. PubChem. Melatonin [Internet]. Nih.gov. [cited 2021 Apr 16]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Melatonin (188)

4.2. Non-pharmacological methods

Acupuncture is a potential, new method of improving postoperative sleep in patients (171, 172). Studies suggest that acupuncture might improve sleep quality in patients with primary insomnia (173).

Light and noise in the ICU might be an important contributor to postoperative sleep disturbances. Huang et al. found that ICU conditions, specifically noise and light, produce disturbances in nighttime sleep and melatonin production. Their study demonstrated that use of earplugs, eye masks and oral melatonin improved sleep quality in healthy patients sleeping in simulated ICU environment (174). Bani Younis et al. also reported that use of eye masks and earplugs in ICU patients improved their quality of sleep (175).

5. Conclusion

The mechanism and scope of action of general anesthetics remains largely unexplained. Studies have shown numerous links between general anesthesia and sleep, as well as the potential influences of general anesthesia on postoperative sleep. Postoperative sleep is essential to patient wellbeing and recovery. Compromising its quality is associated with various postoperative complications which makes the precise extent to which it is influenced by general anesthesia an important question. There are very few studies that examine the isolated effects of general anesthesia on sleep without the contributing surgical factors. Although advances in better understanding this topic have been made, further research is needed to provide full clarity on this matter.

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8. Biography

Matea Mataković Trivunčević was born on the 13th of February, 1997 in Zagreb. She graduated from the II. Gymnasium in 2015 and enrolled in the University of Zagreb Medical School in the same year, which she is currently attending. During her studies she volunteered at the University Hospital Centre Sisters of Mercy Zagreb at the Traumatology Clinic, Clinical Hospital Sv. Duh (Department of Orthopedics) and at the University Hospital Centre Zagreb (Department of Traumatology, Department of Anesthesiology, Reanimatology and Intensive Care). She is an active member of the Student Organization of Anesthesiology.