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PRACA POGLĄDOWA
REVIEW

The impact of anesthetics on the transcriptome

Wpływ anestetyków na transkryptom

Anna Pilarz[1], Joanna Brzoza[1], Marcin Tomsia[2]

[1]Students' Scientific Club at the Department of Forensic Medicine and Toxicology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

[2]Department of Forensic Medicine and Toxicology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ABSTRACT

Anesthetic agents are routinely used as a crucial component of many procedures, but little is known about the long-term effects of their use. Anesthetics vary in their efficacy and the frequency of adverse effects depending on their mechanism of action. The aim of the study is to review the latest literature on the impact of anesthetics on the transcriptome and the human body. A wide range of variations arising from the use of anesthetics has been presented, along with their effects that may extend beyond the perioperative period. Certain functions of anesthetics in the cancer process have been outlined, such as increasing and decreasing gene expression as well as weakening components of the immune system. The promising role of local anesthetics in reducing cancer recurrence has been highlighted. The issue of exposure among large groups of professionals working in operating rooms and clinical departments has also been described. Studies have confirmed that anesthetics are not neutral for the human body; they affect the immune system, may exert pro-tumorigenic effects, influence cell proliferation and differentiation, additionally play a role in tumor growth and the development of metastases. New research on the effects of anesthetic drugs is necessary. The results of these studies may provide new therapeutic targets in cancer cells, and well-chosen therapy could increase the safety of clinical prognosis, reduce the potential occurrence of behavioral and neurocognitive disorders, and decrease the spread of metastases.

KEYWORDS

anesthetics, inflammatory cytokines, gene expression, induction of apoptosis factors, oncogenesis

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Address for correspondence: dr. n. med. Marcin Tomsia, Katedra i Zakład Medycyny Sądowej i Toksykologii Sądowo-Lekarskiej, ul. Medyków 18, 40-752 Katowice, tel. +48 32 208 86 78, email: mtomsia@sum.edu.pl

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STRESZCZENIE

Środki znieczulające są rutynowo stosowane jako kluczowy element wielu zabiegów, niewiele jednak wiadomo o długotrwałych skutkach ich stosowania. W zależności od mechanizmu działania anestetyki różnią się pod względem skuteczności i częstości występowania działań niepożądanych. Celem badania jest przegląd najnowszej literatury na temat wpływu środków znieczulających na transkryptom i organizm człowieka. Przedstawiono szeroki zakres zmian powstających w wyniku stosowania anestetyków, a także ich działanie mogące wykraczać poza okres okołooperacyjny. Przybliżono pewne funkcje anestetyków w procesie nowotworowym, takie jak zwiększenie i zmniejszenie ekspresji genów czy osłabienie elementów układu odpornościowego. Podkreślono obiecującą rolę środków miejscowo znieczulających w ograniczaniu nawrotów nowotworu. Opisano również problem narażenia dużych grup specjalistów pracujących na salach operacyjnych i oddziałach klinicznych. Badania potwierdziły, że anestetyki nie są obojętne dla ludzkiego organizmu; wpływają na układ immunologiczny, mogą wywierać działanie rakotwórcze, wpływać na proliferację, różnicowanie komórek, a także odgrywać rolę we wzroście guza i rozwoju przerzutów nowotworowych. Konieczne są nowe badania nad wpływem leków znieczulających. Wyniki tych badań mogą zapewnić nowy cel terapeutyczny, a odpowiednio dobrana terapia może zwiększyć szansę dobrego rokowania klinicznego, zmniejszyć prawdopodobieństwo wystąpienia zaburzeń behawioralnych i neurokognitywnych oraz ograniczyć rozprzestrzenianie się przerzutów.

SŁOWA KLUCZOWE

anestetyki, cytokiny zapalne, ekspresja genów, czynniki indukcji apoptozy, onkogeneza

Introduction

The Lancet reports that each year over 300 million people worldwide receive general anesthesia under various conditions. General anesthesia is routinely used as an essential component of surgical procedures [1]. Increasingly, it is recognized that a significant portion of the beneficial effects of anesthetics has a molecular basis. However, less than 2% of the mammalian genome encodes proteins, which means that more than 90% consists of non-coding RNA responsible for controlling development, differentiation, metabolism, and cell growth. It is widely believed that the regulation of gene expression is required in all kinds of biological processes, including proliferation, differentiation, and the progression of disease in cells [2].

The first microarray study of inhalational anesthetics revealed that the expression of 1.5% of 10,000 genes in various organs was altered. Anesthetic agents are also capable of inducing long-lasting and transgenerational epigenetic effects.

The aim of this study is to present the existing research describing the impact of anesthetics on the transcriptome. The safety of general anesthesia has been assessed and confirmed by numerous clinical studies. However, little is known about its comprehensive effects on the body, including its influence on gene expression. In this paper, we aim to present data regarding this issue [3].

We also refer to studies regarding the influence of sevoflurane on the induction of apoptosis in both normal and cancer cells [4]. Increasing evidence suggests that perioperative factors, including the choice of anesthetic agent, influence cancer recurrence after surgery, although little is still known about the impact of anesthetics on the cancer cells themselves. It is known that certain anesthetic agents affect the signaling mechanisms of hypoxia in healthy cells by activating hypoxia-inducible factors (HIFs). HIFs are also strongly associated with tumorigenesis, and their high levels are linked to a poor prognosis, which we also address in our work [5].

The aim of this study is also to elucidate how individual anesthetics affect the transcriptome and what consequences this has for the whole organism. By means of this comparison, physicians and clinicians can consider the choice of dosage or another anesthetic agent tailored to the procedure. The role of anesthetics appears to have a long-term impact on the functioning of individual systems, and the changes that occur after their use may be irreversible, which should encourage a holistic approach to the patient before the use of any of them. Figure 1 shows the non-operative effects of anesthetics.

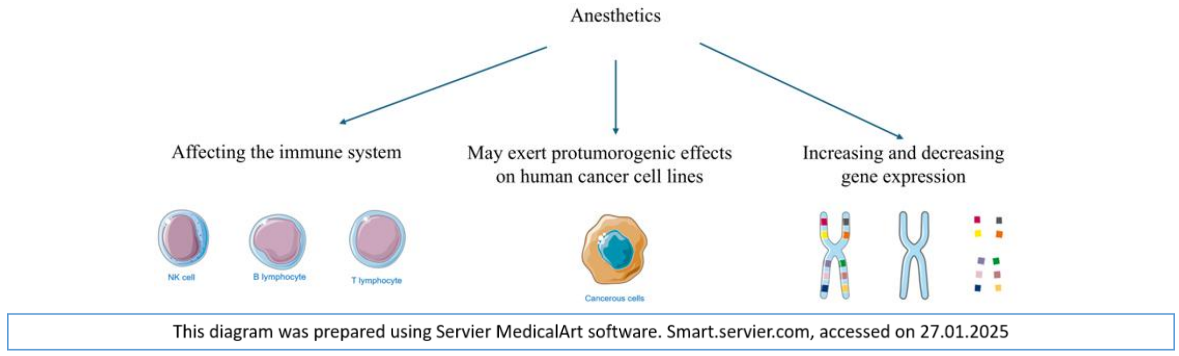

Fig. 1. Non-operative effects of anesthetics.

The literature analysis included a systematic review of scientific and medical literature from the PubMed and Google Scholar databases. After entering three keywords, i.e. "Anesthetics", "Impact", and "Transcript", 583 records were obtained in two databases. After discarding duplicate records, the analysis of 200 works were subjected to substantive analysis, of which 90 were used.

Halogenated anesthetics

Inhaled anesthetics (nitrous oxide, halothane, isoflurane, desflurane, sevoflurane) are administered as the primary therapy for preoperative sedation and to assist in maintaining anesthesia with intravenous (IV) anesthetics (such as midazolam, propofol) during the perioperative period. Inhaled anesthetics are commonly used in clinical practice due to their chemical properties, which allow rapid introduction of the agent into arterial blood through pulmonary circulation compared to the more circuitous route of venous circulation [6].

Scientific research demonstrates a close relationship between halogenated anesthetics and the immune system. Halogenated anesthetics lead to its suppression by affecting the activity of natural killer (NK) and T lymphocytes [7].

Nitrous oxide

Nitrous oxide (N_2O) is a colorless, non-flammable, practically odorless gas. It exhibits anesthetic, analgesic, and sedative effects. In clinical practice, it is not used as a standalone anesthetic for general anesthesia due to its insufficient anesthetic effect. However, it can be combined with other agents to complement or enhance anesthesia. Among the adverse effects of nitrous oxide, a moderate decrease in left ventricular contractility can be observed. Because of its low blood/gas partition coefficient, it is rapidly and completely eliminated through the respiratory tract, and its only metabolic effect is the inactivation of vitamin B_{12}, which affects foliate metabolism, leading to the disruption of DNA synthesis [8].

The diversity of nitrous oxide's targets suggests a complex pharmacological action of this drug. Indeed, treatment with N_2O in a study on mice affected the transcription not only of several genes related to the mitogen-activated protein kinases (MAPK) pathway but also of hundreds of other genes, including synaptic vesicle transport factors (*Apba1*, *Cplx1*, *Stxbp2*, *Syt13*, *Snap25*, *Unc13a*, *Picalm*, *Dnm3*), G protein-binding receptors (*Adgrl1*, *Chrm4*, *Gpr3*, *Htr1a*, *Htr2a*, *Htr6*, *Lpar1*, *Mc4r* and *Ptger4*), ion channels (*Gabra2* and *Gabra3*), postsynaptic scaffolding proteins (*Nlgn2*, *Nlgn3*, *Shank3*) and immediate early genes (*Arc*, *Egr1*, *Egr2*, *Fos*, *Egr4*, *Fosb*, *Junb*, *Klf4*, *Maff* and *Nr4a1*), which may be regulated by neuronal activity and subsequent MAPK activation [9].

In recent years, there has been a significant increase in the recreational use of N_2O, leading to growing concerns regarding its acute and chronic toxicity. There is a wide range of chronic symptoms, including myelopathy, neuropathy, psychiatric symptoms, cognitive impairments, and cardiovascular effects. N_2O interacts with neurotransmitter systems, producing anesthetic, analgesic, anxiolytic, and potentially antidepressant effects, with a potential for dependence [10].

Isoflurane

Isoflurane is an inhaled anesthetic used in the induction of anesthesia following the administration of a short--acting intravenous anesthetic and to maintain general anesthesia.

It has been demonstrated that isoflurane affects the immune system by reducing the activity of NK cells, induces the apoptosis of T and B cells, and decreases the Th1/Th2 ratio [11].

The commonly used anesthetic may also exert pro--tumorigenic effects on human cancer cell lines. It stimulates a cellular signaling pathway involving HIF, which is implicated in tumorigenesis and enhances cellular activities associated with a malignant phenotype. This occurs in a time- and dose-dependent manner, independent of oxygen, through the PI3K/Akt/mTOR pathway, resulting in de novo

synthesis of HIF, nuclear translocation, and the transcription of target genes. It thus promotes the growth of kidney cancer cells and has a noteworthy impact on the malignancy potential of cells [12].

Halothane

Halothane is a clear, heavy, and colorless liquid with a sweet and non-irritating odor. Its structure resembles an alkane. In 1956, halothane was introduced into clinical practice, but it caused fulminant hepatic necrosis, leading to the development of new inhalational agents [13].

The ability of inhalational anesthetics to induce DNA damage has been demonstrated, with halothane being identified as the most harmful in this group of drugs. These findings are consistent with earlier reports indicating that halothane metabolites persist longer in the body (15–20%) compared to sevoflurane (2–5%) and isoflurane (0.2–2%) [14].

DNA damage has also been observed in human peripheral blood lymphocytes in vitro using the alkaline comet assay. DNA strand breaks were dose--dependent on the administered dose of halothane. Halothane proved to be the strongest genotoxic agent, causing about a 5-fold increase in damage at the highest concentrations (100 mM) compared to the lowest (0.1 mM). The genotoxic properties of halothane are attributed to better penetration into cells and epithelial permeation. Additionally, it intensifies neutrophil apoptosis in cells [15].

Sevoflurane

Sevoflurane is an inhaled anesthetic. It is a volatile liquid with a mild odor. It is used for the induction and maintenance of general anesthesia in hospital and ambulatory settings in adults and children [16]. Postoperative cognitive dysfunctions (POCD) are conditions that develop after surgery under anesthesia and lead to deterioration in cognitive function [17]. Nevertheless, the mechanism of POCD still remains unknown. A study aiming to investigate the mechanism underlying the development of POCD during sevoflurane anesthesia in mice showed that it induces inflammation in primary hippocampal neurons by regulating the *Hoxa5/Gm5106/miR-27b-3p* positive feedback loop. Sevoflurane induces inflammation in the nervous system by increasing the expression of long non-coding RNA *Gm5106*, which is transcriptionally activated by *Hoxa5* and directly targeted by *miR-27b-3p*. *Hoxa5*, *Gm5106*, and *miR-27b-3p* form a positive feedback loop in sevoflurane-stimulated inflammation. Nonetheless, in this study, there is still a lack of evidence for the presence of *HOXA5-ABCB1* in human samples. At the current stage of research on *miR-27b-3p*, it is speculated that *Hoxa5* and *Gm5106* serve as biomarkers for sevoflurane-induced POCD [18].

The impact of sevoflurane anesthesia on signaling and metabolic pathways in susceptible cancer cells resulted in increased activity of *CYP2E1*, *caspase-3*, *p53*, and early de novo ceramide synthesis. The rate of apoptosis was higher in cancer cells originating from the gastrointestinal epithelium (16.9% after 24 hours). *HEp-2* laryngeal cancer cells lacking *CYP2E1* exhibited a lower apoptotic rate (7.4% after 24 hours) and a delayed increase in de novo ceramides. It can be suspected that sevoflurane may promote colon cancer cell growth, but this still requires further clinical investigation [4].

Sevoflurane is also widely used in hepatectomy, and there is a study available regarding its impact on the metastasis of hepatocellular carcinoma (HCC). It has been demonstrated that sevoflurane inhibits the migration and invasion of HCC cells in a dose--dependent manner and also suppresses HCC metastasis through *miR-665* [19].

Desflurane

It is the most modern inhalational anesthetic introduced into clinical practice and is characterized by low solubility in blood and rapid emergence from anesthesia. However, desflurane exhibits the highest minimum alveolar concentration (MAC, 6–7%) among halogenated anesthetics, which means that it is not as potent as other modern inhalational anesthetics, necessitating the use of higher concentrations of this agent [20].

As a consequence of desflurane use, there is a systemic increase in inflammatory cytokines IL-6 and IL-8. The increase in IL-6 in response to surgical stress is associated with neutrophilia, the release of adrenocorticotropic hormone, increased production of C-reactive protein, and its sustained elevation is correlated with a poor prognosis in critically ill patients. IL-8 activity is linked with IL-6 post-injury, attracting neutrophils and macrophages to the site of inflammation. During the inflammatory process, the release of reactive oxygen species (ROS) increases, which can damage DNA and other macromolecules. Studies describe a significant increase in DNA damage in the comet assay in patients anesthetized with desflurane and an increased formation of sister chromatid exchanges during desflurane anesthesia up to 7 days post-operation [21].

A subsequent study conducted by the GENOTOX Laboratory on patients undergoing minor procedures with or without N_2O-desflurane revealed a significant increase in the systemic levels of IL-6 and hs-CRP one day after surgery in both groups, as well as prolactin levels intraoperatively compared to the baseline and postoperative values for both groups. From this, it can

be inferred that N_2O does not impair the inflammatory profile or neuroendocrine response compared to patients anesthetized solely with desflurane. Further studies are warranted to compare DNA damage and inflammatory response in surgical patients who undergo desflurane or other inhalational or intravenous anesthetics to observe if one anesthetic is better or worse than the other concerning genotoxicity and inflammation [22].

Intravenous anesthetics

Ketamine, propofol, and thiopental

These are examples of drugs commonly used in intravenous anesthesia. Intravenous anesthetics have anti-inflammatory properties, which are beneficial for patients in most septic cases. Intravenous anesthetics act in multiple ways on the immune system. Ketamine and sodium thiopental decrease the number of helper T cells and natural killer cell activity while increasing the number of suppressor T cells [23]. Sodium thiopental and ketamine inhibit the release of IL-1, IL-6, tumor necrosis factor α (TNF-α), and IL-8. A low dose of ketamine, acting as an antagonist of N-methyl-D-aspartate (NMDA) receptors, shortens the half-life of IL-6 [24,25]. Additionally, these drugs increase the level of IL-10 [26].
Intravenous anesthetics are used to initiate and maintain anesthesia; in the case of total intravenous anesthesia (TIVA), the entire anesthesia process is managed intravenously [27]. In contrast to propofol, ketamine and thiopental inhibit the activity of NK cells. Ketamine induces apoptosis in lymphocytes via the mitochondrial pathway and inhibits the functional maturation of dendritic cells, while thiopental protects T lymphocytes from apoptosis by inducing heat shock proteins [28]. In this scenario, ketamine reduces the synthesis of pro-inflammatory cytokines such as IL-6 and TNF-α. On the other hand, thiopental inhibits neutrophil activity and suppresses the activation of nuclear factor kappa B (NF-κB), leading to the activation of T lymphocytes, secretion of IL-2, IL-6, and IL-8, as well as the overexpression of interferon gamma (IFN-γ) [29]. Ketamine can inhibit the expression of the *CYP* gene by suppressing calcium signaling, reducing ATP levels, generating an excessive amount of reactive oxygen species, and consequently disrupting cytoskeletal dynamics [30].

Ketamine

Ketamine is an antagonist of the NMDA receptor, used since the 1960s as an anesthetic agent, especially in hemodynamically unstable patients. Ketamine has proven to be a desirable drug due to its short half-life and lack of clinically significant respiratory depression. In subanesthetic doses, it exhibits potent analgesic properties without depressant effects on the respiratory and cardiovascular systems [31].
Ketamine inhibits the production of anti-inflammatory cytokines and may also suppress the activity of natural killer cells. It can induce apoptosis in lymphocytes and inhibit the functional maturation of dendritic cells [32]. Ketamine also exhibits anti-inflammatory effects, which may be associated with inhibiting the production of TNF by macrophages in the presence of bacteria [33]. Studies also describe that ketamine and sodium thiopental have a detrimental effect on mast cells in patients at a high risk of infection [34].

Sodium thiopental

Sodium thiopental is a rapidly acting intravenous anesthetic agent that acts on gamma-aminobutyric acid sub-type A receptors (GABA-A receptors), confirming their presence in immune system cells. Comparing the effects of propofol and sodium thiopental on the Th1/Th2 balance, by measuring the levels of IFN-γ, IL-4, and IL-2, it was shown that sodium thiopental reduced the concentration of IFN-γ and IL-4 without affecting the concentration of IL-2 [35].
In the case of intravenous administration in children and adolescents, there is significant variability in the required dosage. This necessitated a higher range of doses for children not previously medicated. Thiopental was withdrawn from the United States market in 2011, mainly due to its illegal use in the United States as a drug for lethal injections [36].

Propofol

A strongly and rapidly acting intravenous anesthetic inducing a dose-dependent loss of consciousness. The drug provides rapid induction, good control of the sedation level, and quick recovery of consciousness upon the discontinuation of infusion. Propofol has antioxidant and anti-inflammatory properties by inhibiting the production of prostaglandins and inflammatory cytokines as well as inhibiting cyclooxygenase activity [37].
Data on whether propofol anesthesia increases or decreases IL-6 levels are inconclusive. In vitro, propofol inhibits IL-6 production by means of stimulated lipoproteins and reduces the levels of cytokines IL-1, TNF-α, and IL-6. Literature also describes research results indicating that propofol increases IL-10 levels. Higher levels of anti--inflammatory cytokines in patients receiving propofol are the reason behind its anti-inflammatory properties. The administration of a high dose of propofol increases the IFN-γ/IL-4 ratio, while a low dose of propofol does not change the cytokine levels [38].
Propofol has a different mechanism of action than sodium thiopental; it relies on its anti-inflammatory

action, inhibition of COX-2, reduction of PGE-2, and decrease in pro-inflammatory cytokines [39].
The impact on *ADRB2* gene expression during propofol sedation for abdominal surgery has been investigated. An increase in *ADRB2* gene expression, responsible for stimulating the sympathetic nervous system and the cardiovascular system, has been described. Its application in regulating the clinical prognosis and treatment resistance is also demonstrated [40].
Additionally, a groundbreaking discovery regarding propofol was made in a study conducted by Zhao and Mo [41], where a significant decrease in subsets of T lymphocytes and NK cells during general anesthesia was described.
General anesthesia induced by propofol triggers phase shifts of circadian rhythms controlled by the suprachiasmatic nucleus (SCN) only at specific times of day (late rest period and early activity period). General anesthesia induced by propofol is associated with later reductions in the *Per2* mRNA levels throughout the brain. Short-term anesthesia induced by propofol leads to transient reductions in *Per1* and *Per2* expression in the SCN. These acute effects known from behavioral arousal and dark impulses play a role in the resetting properties of non-photic signals. Interestingly, even though treatment with exogenous melatonin can modify the SCN clock, as does propofol anesthesia, the initial molecular targets are not *Per* genes, but *Rev-erbα* and *Rorβ*. These data suggest that propofol anesthesia combines the activation of common SCN transduction pathways with classical non-photic signals and dark impulses, but not with pharmacological doses of melatonin [42].

Opioids

Morphine

Morphine belongs to the group of potent analgesic drugs known as opioids, also called narcotic analgesics. It is an alkaloid derived from opium and a derivative of phenanthrene. Morphine inhibits the activity of NK cells, promotes lymphocyte apoptosis, reduces T cell differentiation, and stimulates angiogenesis [43].
Morphine activates glial cells, leading to the release of cytokines, including IL-1β, IL-6, and TNF-α, which counteract the analgesic effects of morphine. The release of cytokines is not associated with the frequency and timing of morphine administration. Considering the short-term cytokine response to morphine (about 5 minutes), it can be assumed that morphine rather stimulates the release of stored cytokines than synthesizes them [35].
The study by Shavit et al. [44] suggests that IL-1 may reduce the analgesic effects induced by morphine. The authors also noted that IL-1 plays an important role in morphine tolerance. On the other hand, researchers discovered that IL-1β affects the expression of opioid receptors in glial cells, and IL-1β may regulate opioid receptors (μ, δ, and K) in astrocytes [45].
Studies have also shown that clinically relevant doses of morphine led to an increase in tumor volume and tumor vascularization. Endogenous μ-opioid receptor (MOR) ligands, endomorphin-1 and endomorphin-2, enhance angiogenesis in addition to the proliferation, migration, and adhesion of endothelial cells in vitro, effects that were reversed by the MOR antagonist, naltrexone [46].
The next study related to the developing tolerance to morphine after long-term use revealed an increased expression of *CircNf1* as well as decreased levels of *miR-330-3p* and *miR-665* in rats treated with morphine. The investigation revealed an increased expression and downregulation of *CircNf1*, *miR-330-3p* and *miR-665* in rats chronically treated with morphine, suggesting that increased *circNf1* and *CXCL12* expression mediates the development of morphine analgesic tolerance [47].
Scientists found that prolonged exposure to morphine and the development of tolerance are associated with the overexpression of *MRAK159688*, which enhances the expression and function of REST, thereby inhibiting the expression of the MOR and subsequently inducing morphine tolerance [48].

Fentanyl, sufentanil, alfentanil, remifentanil

Opioid analgesics are administered during surgery to alleviate pain (inhibit nociceptive signaling). In intraoperative anesthesia, piperidine derivatives are commonly prescribed. In Poland, the most frequently used medication from this group is fentanyl, although for several years now, remifentanil and sufentanil have also been available [49].
Fentanyl and sufentanil reduce the activity of NK cells and increase the number of regulatory T lymphocytes. Alfentanil, along with remifentanil, decreases NK cell activity, while remifentanil additionally inhibits lymphocyte proliferation [33].

Fentanyl

The immune response changes during the perioperative period. Fentanyl exhibits cytotoxicity towards NK cells. Researchers reported that fentanyl inhibits NK cell activity in mice [50]. Beilin et al. [51] found that 24 hours postoperatively, NK cell activity decreased at both low and high doses of fentanyl. During the first 24 hours after surgery, a rapid increase in NK activity was observed, after which there was a significant decrease in NK activity that returned to the baseline values after 8 days. Pain medications exhibit specific effects, with fentanyl reducing NK cell activity both postoperatively and in the absence of surgery.

Fentanyl in the conducted study demonstrated the ability to induce autistic-like behaviors by reducing the expression of *Grin2b*. Further research is necessary to determine the potential clinical significance for autism risk [52].

Local anesthetics

Lidocaine, ropivacaine, bupivacaine

Currently, local anesthetics are widely used in various fields of medicine with diverse application possibilities. The frequent use of local anesthetics cannot be without an impact on the increased likelihood of adverse effects of these agents, including hypersensitivity reactions [53].

Lidocaine, ropivacaine, and bupivacaine inhibit cell proliferation and differentiation, are cytotoxic to mesenchymal stem cells in vitro, and play a key role in tumor growth as well as metastasis development in cancer cells [54].

Locally administered lidocaine inhibits the receptor of the epidermal growth factor, which is a target molecule for many anticancer drugs. A study assessing the direct impact of local anesthetics showed that lidocaine and bupivacaine induce apoptosis in cancer cells both in vivo and in vitro, suggesting potential benefits in oncological surgery [55].

A study has shown that local lidocaine increases the activity of NK cells against cancer in vitro by releasing lytic granules [56].

Each of the drugs leads to an increase or decrease in the expression of genes. We present the previous discoveries of these genes in Table I.

Table I. Increase or decrease in expression of previously discovered genes after administration of specific anesthetic

Drug name	Increase in expression	Decrease in expression	Author	Year of study
Isoflurane	*HIF*	–	Benzonana et al. [5]	2013
Halothane	*HMGCS2*	*KRT31*	Wang et al. [74]	2023
Sevoflurane	*PARP-1*	*miR-27b-3p*	Zhu and Ma [18]	2021
	Gm5106			
	Hoxa5			
Desflurane	IL-6	–	Arruda et al. [22]	2019
	IL-8			
Thiopental	–	*NF-κB*	Chen et al. [30]	2018
Propofol	–	*Per-1* *Per-2*	Ben-Hamouda et al. [42]	2018
	ADRB2	–	Lin et al. [40]	2023
Morphine	*CircNf1*	*miR-330-3p*	Bai et al. [47]	2023
	MRAK159688	*miR-665*	Deng et al. [48]	2022
Fentanyl	–	*Grin2b*	Sheng et al. [52]	2022

HIF – hypoxia-inducible factor; IL-6 – interleukin 6; IL-8 – interleukin 8.

The involvement of laboratory animals in research on the role of anesthetics

Sevoflurane is the most commonly used inhalational anesthetic in general anesthesia. A whole-genome transcription analysis was conducted on the brains of mice exposed to sevoflurane. The results of the analysis suggest that sevoflurane induced both angiogenesis and the appearance of undifferentiated nerve cells in all the sampled brain regions. These changes in gene expression were not observed in the brains of sleeping mice and appeared to be specific to brains exposed to sevoflurane. The level of transcription factor *Klf4* was increased in all the brain samples, and the results of pathway and motif analysis suggest that *Klf4* is a key regulator of angiogenesis in addition to the appearance of undifferentiated nerve cell transcription [57]. The effect of sevoflurane on nerve cell transcription in mice is illustrated in Figure 2.

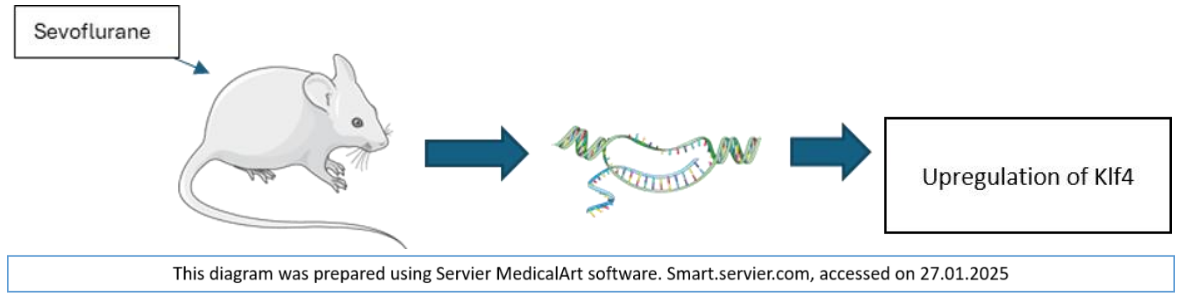

Fig. 2. Effect of sevoflurane on nerve cell transcription in mice.

Additionally, reduced DNA methylation in the promoter region of *Arc* and *JunB* – genes involved in synaptic plasticity and neuronal development – along with increased expression of their mRNA in rats exposed to six hours of sevoflurane exposure, is inherited transgenerationally in male offspring. These modifications to components crucial to synaptic plasticity could partially contribute to morphological and cognitive deficits known to occur with neonatal sevoflurane exposure. Further studies are required to directly link the observed epigenetic modifications and dysregulation of immediate early genes to anesthesia--induced neurotoxicity, synaptic morphological and a myriad of behavioral deficits [58].

The relationship between anesthetics and neurons

An important topic in many scientific studies is the impact of anesthesia in pediatric anesthesia. In humans, synaptogenesis begins in the third trimester of pregnancy, and rapid brain growth continues from 2 to 3 years after birth. Importantly, as part of normal brain development, up to 50% to 70% of neurons and progenitor cells undergo physiological cell death and cell elimination through an inherent programmed cell death process called apoptosis, which centers around the caspase enzyme family [59,60,61]. The diverse group of clinically used agents for general anesthesia includes intravenous anesthetics such as benzodiazepines, barbiturates, ketamine, propofol, and etomidate, as well as inhalational anesthetics such as halothane, isoflurane, sevoflurane, desflurane, nitrous oxide, and xenon. Although these compounds are chemically very different, their mechanism of action inhibiting neuronal activity is very similar, involving various degrees of changes in synaptic transmission involving γ-aminobutyric acid (GABA) and/or NMDA receptors [62]. Since neuronal activity mediated by GABA and NMDA is essential for mammalian brain development, exposure to general anesthetics may potentially disrupt normal brain maturation [63]. Studies describing structural brain abnormalities in children after anesthesia have not been found.

General anesthetics commonly administered during anesthesia necessarily modulate neuronal activity and may have effects beyond the perioperative period. The negative effects of anesthetics are more apparent in populations with reduced stress coping abilities, such as older individuals, in whom persistent neuronal dysfunction may manifest as memory or cognitive function deficits or the exacerbation of chronic neurodegenerative diseases. POCD develops in ~10–40% of patients, with risk factors including (among others) older age, the occurrence of perioperative complications, and pre-existing cerebrovascular disease. Determining the role of anesthetics is challenging owing to the chronic, typically slow, and progressive course of the disease process [64].

Anesthetics and the oncogenic process

Cancer is the second leading cause of death in developed countries, with the majority of deaths caused by metastasis. Surgery is the gold standard in treating most cancers. Nevertheless, tumor surgery can lead to the release of cancer cells into the systemic circulation. Surgical stress and several perioperative factors are suggested to accelerate tumor growth, thereby raising the risk of metastatic recurrence. The anesthetic technique may influence the neuroendocrine and immune response of the patient during surgery [29].

While surgical stress and pain can activate neuroendocrine cascades that inhibit NK cells perioperatively, anesthetics and analgesics (which alleviate pain and the stress response) may also independently suppress immune functions. This is because anesthetics weaken nearly all components of the immune system: cellular and humoral, in both humans and animals, both in vivo and in vitro [65].

The impact of propofol, thiopental, ketamine, and halothane was investigated: all the drugs reduced the number of circulating NK cells, and all except propofol reduced the cytotoxicity of NK cells [66]. Although opioids are effective pain relievers, there is increasing evidence that they may have negative consequences for individuals undergoing oncologic surgeries. Administering morphine to mice in clinically relevant doses leads to increased angiogenesis and breast tumor growth [67].

However, the interaction of opioids with the immune system is complex: perioperative morphine

administered to rats undergoing a laparotomy attenuated the surgical stress-induced tumor-retaining effect, particularly when administered before surgery [68].

Morphine promoted cell death and apoptosis in the adenocarcinoma cell line. Moreover, endogenous and exogenous opioids have distinct immunomodulatory properties, partially explained by their affinity for different subtypes of opioid receptors [69].

Data on N_2O was also provided, as demonstrated in an in vivo model, N_2O inhibits chemotaxis, which is potentially the strongest stimulator of metastatic development in the liver and lungs after surgery [70]. Patients receiving perioperatively β-adrenolytics have a lower frequency of metastatic recurrences after surgery. Additionally, a continuous infusion of propofol may inhibit the development of lung metastases [71].

Researchers observed that one-year survival was nearly 10% higher in oncologic surgeries where propofol was used as the anesthetic agent [72]. Another study assessing the direct impact of local anesthetics showed that lidocaine and bupivacaine induce apoptosis in cancer cells both in vivo and in vitro, suggesting potential benefits in oncologic surgery. These drugs may possess a new ability to reduce metastatic spread in cancer. Differential gene expression was demonstrated after ex vivo exposure of the *SH-SY5Y* brain cancer cell line and the *MCF-7* breast cancer cell line to enflurane, isoflurane, desflurane, halothane, sevoflurane, and nitrous oxide. Sevoflurane inhibits the viability, invasion, migration, and apoptosis of colorectal cancer cells in a dose-dependent manner by regulating the *circ-HMGCS1/miRNA-34a-5p/SGPP1* axis through the inactivation of *Ras/Raf/MEK/ERK* signaling and regulation of the *ERK/MMP-9* pathway through the upregulation of *miRNA-203* and regulation of the *miRNA-34a/ADAM10* axis. The study also showed a differential and specific impact on circulating exosomal miRNA during the surgical resection of colon cancer. Other anesthetics, such as nonsteroidal anti-inflammatory drugs, propofol, and ketamine, may also modulate epigenetics. Celecoxib inhibits the proliferation, migration, and invasion of osteosarcoma cells through *miRNA-34a*. Lidocaine in clinical concentrations (1 mM) induced DNA demethylation for 120 hours in *BT-20* and *MCF-7* breast cancer cells in vitro. Lidocaine also reduces the proliferation of *PaTu8988t* pancreatic cancer cells after 48 hours in vitro [73].

μ-opioid receptor agonists (MORAs) are indispensable for analgesia in bladder cancer (BC) patients, both during surgery and for chronic pain treatment.

Mouse models of hematogenous metastasis and in situ BC demonstrated that tumor metastasis was significantly increased after MORA treatment. A significant increase in the number of mesenchymal and/or epithelial circulating tumor cells (CTCs) was detected after MORA treatment in both the mouse models and clinical trial patients. Mechanistically, MORAs facilitated the formation of CTCs by activating the MOR/PI3K/AKT/Slug signaling pathway, thereby promoting the epithelial--mesenchymal transition (EMT) of BC cells, as the knockdown of MOR, Slug or blockade of PI3K inhibited the EMT process and CTC formation [74]. Influence of MORA on metastasis is illustrated in Figure 3.

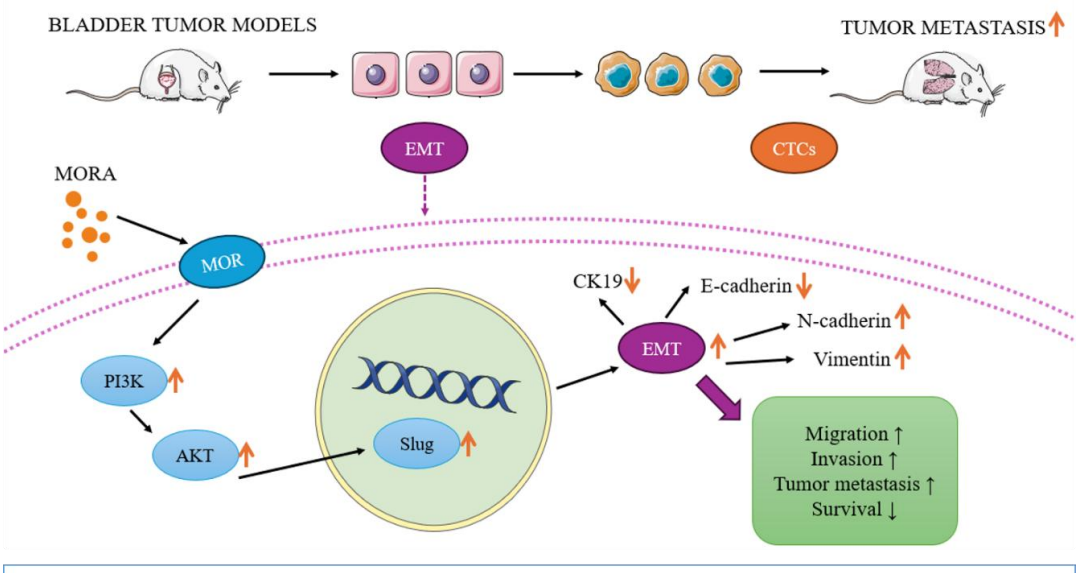

Fig. 3. Influence of μ-opioid receptor agonist (MORA) on metastasis. EMT – epithelial-mesenchymal transition; CTCs – circulating tumor cells; MOR – μ-opioid receptor; PI3K – phosphoinositide 3-kinases; AKT – protein kinase B.

Cancer recurrence

The main available studies evaluated regional and general anesthesia, showing that local or epidural anesthesia does not affect outcomes related to the progression of breast cancer (2132 patients), lung cancer (400 patients), or breast and abdominal cavity cancer (1802 patients). These studies seem to definitively suggest that local anesthesia-analgesia does not reduce the frequency of recurrences after potentially curative cancer surgery [73].
Nonetheless, these studies were not designed to detect differences between the cancer subtypes or the cancer stage. In one study, only 13.5% and 12.5% of patients in the general anesthesia and epidural groups, respectively, had advanced cancer [T3-4], while another study included multiple types of tumors (gastrointestinal, hepatobiliary pancreatic, and urogenital systems, as well as other tumors) [75,76,77].

Breast cancer

In the largest controlled randomized trial (The Breast Cancer Recurrence Trial – BCR), spinal anesthesia was compared with general anesthesia for breast cancer surgery. It included 2132 patients and showed no differences in tumor recurrence and survival between the anesthetic techniques. Unlike the research hypothesis based on residual disease, this trial included only low-stage disease, which has two implications. Firstly, surgery achieves a high cure rate (> 90%) after five years in low-grade disease, as demonstrated in the Mindact study. Secondly, surgery is less invasive in these cases, leading to a reduced stress response, less pain and opioid use, and a lower risk of recurrence [75].
A meta-analysis of six randomized controlled trials compared the impact of propofol-based anesthesia and inhalational anesthesia on postoperative immune function in breast cancer patients, with selected indicators of immune function limited to the cellular level. The results showed no difference in the effect on T lymphocytes between propofol anesthesia and inhalational anesthesia at the end of surgery and 1 day after surgery, but on the postoperative day, the patients anesthetized with propofol had higher CD4+ cell activity and CD4+/CD8+ ratio than those with inhalational anesthesia. Propofol may enhance antitumor immunity by increasing the activity of CD8+ T lymphocytes [78], which may retain lymphocyte activity. The results of the impact of propofol and inhalational anesthetics on subsets of T lymphocytes suggest that propofol may have potentially beneficial effects on the long-term prognosis after breast cancer surgery [79].

Pancreatic cancer

A challenge that may overshadow the effect of anesthesia and reduce enthusiasm for further research is surgical curability, which is now high, especially for low-grade malignancies [80]. On the other hand, the main cause of death from postoperative cancer is metastasis, which occurs in one-third of operated patients [81]. Only a small number of pancreatic cancer patients are eligible for surgery, and among them, 7% will survive for 5 years, indicating a high rate of recurrence and a lack of effective treatment methods [82]. It is well known that epigenetic mechanisms drive the development of pancreatic cancer. For these reasons, studies on epigenetics and pancreatic cancer with different anesthetics may be a promising area of research [83].

Occupational exposure to anesthetics

It is estimated that each year, over 312.9 million surgical procedures are performed worldwide, and the majority of them are conducted under general anesthesia, which can be administered via inhalational or intravenous agents [84]. Therefore, millions of professionals working in operating rooms (OR) and post-anesthesia care units (PACU) are exposed to trace amounts of inhalational anesthetics during their work. Hence, evaluating the potential toxic effects of anesthetics in humans is of paramount importance. Previous studies have shown that occupational exposure to waste anesthetic gases (WAGs) is not associated with oxidative stress or an inflammatory state assessed in serum/plasma, DNA damage assessed in lymphocytes and leukocytes, or molecular modulation assessed in peripheral blood cells in university anesthesiologists [85]. The latest available studies have documented few adverse effects associated with WAGs when permissible exposure values in the workplace are implemented. Specific measures include effective ventilation and purification systems, the regular monitoring of gas concentrations in the air to ensure they remain below the recommended limits, ensuring the proper maintenance of anesthesia equipment, avoiding desflurane and N_2O whenever possible, in addition to minimizing fresh gas flow rates (e.g. using low-flow anesthesia).
An alternative to inhalational anesthesia may be TIVA. Although TIVA is not associated with a risk of occupational exposure or air pollution inherently linked to volatile anesthetic gases, the clinical considerations should be taken into account when choosing an agent. To minimize the potential negative environmental impacts, appropriate procedures for disposing of intravenously administered anesthetic agents should be followed [86].

The role of anesthetics in toxicology

Anesthesia-related death is one of the most complex events to investigate in forensic pathology due to its rarity. Particularly emphasized are the challenges in

determining the cause of death in such circumstances [87].

Each year in the United States, anesthesia/anesthetics are reported to be the primary cause of approximately 34 deaths and contributory factors in an additional 281 deaths, with the risk of death being higher in older individuals and males [88].

A screening method for detecting fentanyl and its analogs in biological samples has been developed and validated. Fentanyl and its analogs are present in biological material at very low concentrations, not exceeding a few nanograms per milliliter or gram. The liquid chromatography-mass spectrometry (LC/MS) technique was employed. The method is characterized by limits of quantification (LOQ) and limits of detection (LOD) ranging from 0.6 to 2 ng/ml and from 0.2 to 0.6 ng/ml, respectively, for the four compounds mentioned above. This method was applied to detect fentanyl in three forensic cases. Blood, bile, and lung blood were collected during the autopsies of individuals who died shortly after surgical procedures where fentanyl was used as the adjunctive general anesthesia [89].

Conclusions

Anesthetics are commonly used drugs with confirmed safety. However, they are not neutral to the human body, affecting the immune system (including reducing NK cell activity, inducing the apoptosis of T and B cells), and may exert pro-tumorigenic effects on human cancer cell lines. Suspicion of the toxic effects of nitrous oxide requires further research, especially considering the increasing popularity of recreational N_2O use among the population.

Local anesthetics may influence cell proliferation and differentiation, are cytotoxic to mesenchymal stem cells in vitro, and may play a key role in tumor growth and metastasis development in cancer cells. The precise action of these agents also requires further research.

Recent interest in the potential impact of anesthesia and analgesic treatment regimens on the transcriptome, as well as their influence on cancer recurrence and metastasis, in addition to their effects on the immune system, suggests that in healthy patients, these effects are not significant. Moreover, in the context of short--term surgeries, the observed changes in the immune system are primarily attributable to the surgical procedure itself. In patients with immune deficiencies, the use of anesthetics may lead to disease progression with long-term drug administration. These agents used in the perioperative period can modulate the innate and acquired immune system, inflammatory response, and angiogenesis, which may affect tumor recurrence and the long-term prognosis. Nevertheless, this issue requires further research to draw additional conclusions.

Promising results also come from studies on reducing the spread of cancer cells and limiting the formation of metastatic lesions, suggesting the potential benefits of using anesthetics and analgesics in oncology, which requires further research.

New studies on the effects of anesthetics on cancer genetics are necessary. The results of these studies may provide an answer as to whether data from animal models and in vitro studies will be applicable in clinical practice, and these studies may provide a new therapeutic target in cancer cells.

MORAs promote BC metastasis by facilitating the formation of CTC. The EMT-CTC axis could be targeted for preventive measures during MORA treatment to inhibit the associated tumor metastasis or recurrence in BC patients.

Therefore, further research on the long-term effects of anesthetic and opioid use is necessary to better understand the potential risks and benefits of their use. There is also a need to develop new anesthesiologic strategies that are safer and more effective.

Authors' contribution

Study design – A. Pilarz, J. Brzoza, M. Tomsia
Data collection – A. Pilarz, J. Brzoza
Manuscript preparation – A. Pilarz, J. Brzoza, M. Tomsia
Literature research – A. Pilarz
Final approval of the version to be published – A. Pilarz, J. Brzoza, M. Tomsia

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