The impact of anaesthetics on immune function

Dr Koichi Yuki and his team at the Boston Children's Hospital investigate the impact of anaesthesia on the immune system. Their research demonstrates that these medications, besides inducing anaesthesia, can also impact immune function. Not only that, but anaesthetic use could even worsen particular diseases during surgery, such as sepsis.

Surgical operations are usually performed under anaesthesia – an artificially-induced insensitivity to pain. There are different types of anaesthesia such as regional and general anaesthesia. Regional anaesthesia blocks nerve impulses from painful stimulation within a certain area while the patient retains consciousness and awareness. General anaesthesia, on the other hand, induces a state where the patient loses awareness and sensation of pain all over the body.

ANAESTHESIA IN SURGERY

A variety of medications can be used to induce this general anaesthesia, called general anaesthetics, with most administered to patients intravenously or via inhalation. Medications that are given inhalationally are termed inhalational (volatile) anaesthetics and are a popular choice of drugs in surgery. Nonetheless, besides inducing anaesthesia, the effects of these drugs on the human body are often poorly understood. Interestingly, research is now showing evidence of interactions between anaesthetics and receptors/other proteins in the body's immune cells.

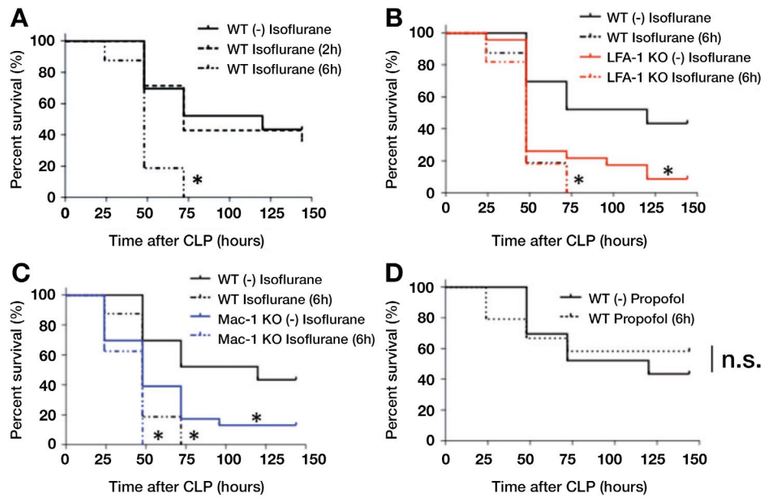

Figure 1. The impact of isoflurane exposure on mortality in experimental polymicrobial abdominal sepsis. A–C, The outcomes of polymicrobial abdominal sepsis induced by CLP in WT mice without isoflurane exposure (n¼25), with isoflurane exposure for 2h (short exposure, n¼14) and 6h (long exposure, n¼20), LFA-1 KO mice withoutisoflurane exposure (n¼24), LFA-1 KO mice with isoflurane exposure for 6h (n¼16), Mac-1 KO mice without isoflurane exposure (n¼24) and Mac-1 KO mice with isoflurane exposure for 6h (n¼15) are shown. D, The outcomes of mice after CLP in WT mice with propofol exposure (n¼20) or without propofol exposure (n¼20) for 6h.Statistical significance was evaluated using Log-rank test. * and ** represent P < .05 and .01, respectively versus WT without isoflurane (or propfol). CLP, cecal ligation

ANAESTHETICS AND THE IMMUNE SYSTEM

The immune system is a highly complex network of cells, organs and tissues that protects our body from foreign intruders like bacteria, viruses or fungi. Early research by Dr Yuki demonstrated that isoflurane and sevoflurane (commonly used volatile anaesthetics) can directly bind to and impair functions of a receptor (adhesion molecule) present on immune cells, called leukocyte function-associated antigen-1 (LFA-1). Isoflurane also impairs another adhesion molecule receptor macrophage-1 antigen (Mac-1).

LFA-1 is a surface protein present on all leukocytes. These are crucial cells in mediating various immune responses including leukocyte migration and immunological synapse formation. Mac-1 is present on a subclass of leukocyte, mostly innate immune cells. It mediates their recruitment and is involved in clearance of microbes and cell debris (through a process known as phagocytosis).

Dr Yuki and his team study the effect of these volatile anaesthetics on the immune system using two examples: destruction of tumour cells by immune cells, and sepsis which is a disease caused by dysregulated immune responses leading to a systemic inflammatory response upon infection.

ANAESTHETICS WORSEN SEPSIS

In addition to systemic inflammatory response, sepsis often causes life-threatening organ dysfunction. Severe sepsis and septic shock remains a health care burden and carries a significant high morbidity and mortality. It has a mortality rate of 20–30% and, in the US alone, around 750,000 cases of sepsis occur annually. More worrying though, these numbers are increasing worldwide. Sepsis is considered to be a time-sensitive disease and requires an urgent or emergent treatment upon diagnosis. Evaluation of

the source of infection is one of the main treatment modalities. The removal of infected fluids or tissue is often performed under general anaesthesia using volatile anaesthetics.

In their recent research, Dr Koutsogiannaki (Instructor in Anaesthesia, Harvard Medical School), one of Dr Yuki's lab members, demonstrated a negative effect of the volatile anaesthetic isoflurane on sepsis outcomes. LFA-1, the receptor shown to be affected by isoflurane *in vitro*, is important for recruitment of neutrophils (a subclass of leukocytes), the first-defence innate immune cells to inflamed tissue.

Proinflammatory molecules activate LFA-1 present on neutrophils circulating in the blood stream. Activated LFA-1 then binds to intercellular adhesion molecules (ICAMs), which are present on the surface of cells on the interior of blood vessels (endothelial cells). Subsequently, neutrophils can traffic into the primary site of infection.

Dr Yuki and his team have demonstrated that, after administering isoflurane for six hours, significantly fewer neutrophils were recruited to septic tissue in their mouse model – in line with LFA-1 being hampered by the drug. However, intravenous anaesthetic propofol administration did not affect neutrophil recruitment to the primary site of infection. Similarly, Mac-1 was also hampered by isoflurane, with phagocytosis found to be less efficient and bacterial load higher in various tissues. The researchers also observed an increased mortality rate in septic mice exposed to isoflurane, but not to propofol. Interestingly though, a short isoflurane exposure did not worsen sepsis. Dr Yuki's group postulated that this would be because bacteria grow exponentially and 6-hour exposure of isoflurane would be significantly long enough to attenuate neutrophil function and allow significant bacterial loads. This therefore indicates that the time of exposure to this anaesthetic probably plays an important role as well.

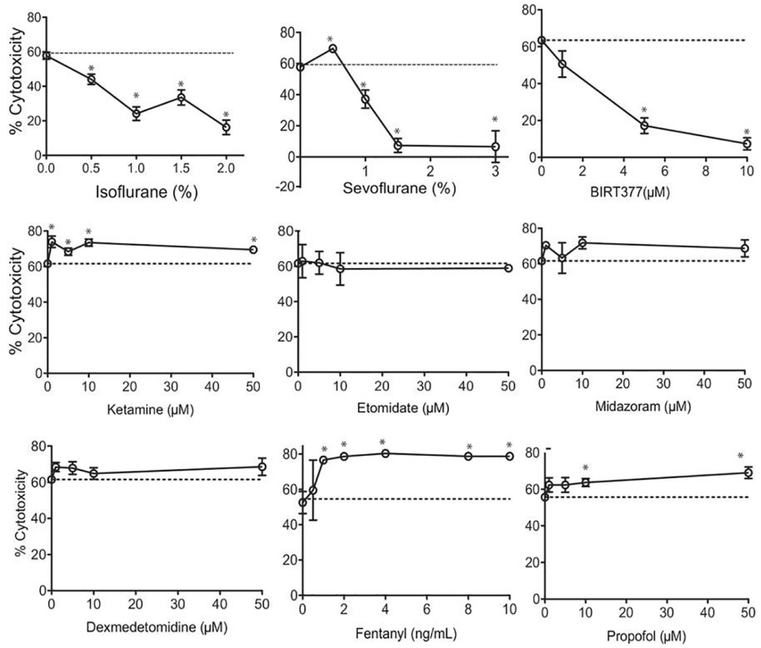

Figure 2. Cytotoxicity of K562 cells by NK92-MI cells was tested under different anesthetics at various concentrations. In addition, the effect of LFA-1 allosteric antagonist BIRT377 was tested. Cells were co-incubated for 4h. Data are shown as mean ± S.D. of 10 replicates for anesthetic experiments and 4 replicates for BIRT377 experiment. Statistical analyses were performed using one-way analysis of variance with Tukey post hoc analysis. *denotes $p < 0.05$ versus mock

ANAESTHETICS PREVENT TUMOUR CELL DEATH

Dr Yuki and his team found that different anaesthetics have different effects on another important set of immune cells called natural killer cells (NK cells). These cells are especially important due to their role in preventing tumour development, through their ability to directly kill tumour cells without being primed beforehand. This function is unlike other immune cells, which instead have to produce highly specific surface receptors in order to be able to recognise and kill target cells.

Activated NK cells release toxic substances from cellular vesicles into their target cells, which, in turn, not only induces cell death, but also produces signals that stimulate a more specialised immune response. Interestingly, LFA-1 is one of the crucial activation receptors on NK cells and is also involved in binding to target tumour cells. Therefore, given that LFA-1 is affected by the volatile anaesthetics isoflurane and sevoflurane, Dr Yuki and his team have investigated the effect of these anaesthetics on NK cell function. By exposing co-cultured tumour and NK cells to isoflurane and sevoflurane, Dr Yuki and his team found that the tumour cell toxicity induced by NK-cells was reduced, as theorised. More specifically, the binding of NK-cells to their targets and the localisation of the cytotoxic vesicles within the NK cells was negatively affected.

IMPROVING PATIENT CARE

Anaesthetics are typically administered to patients regardless of the type of disease being treated during surgical operations. However, as Dr Yuki's research proves, anaesthetics can affect immune functions and certain drugs might not be suitable for anaesthetising patients with certain disease states. His findings also provide incentives for patient-based studies, which will be necessary to finalise conclusions on optimal patient care.

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Q&A

Why did you first become interested in this area of research?
In our anaesthesia practice at Boston Children's Hospital, volatile anaesthetic isoflurane is the mainstay of anaesthetic agents for paediatric cardiac surgery, including when we use cardiopulmonary bypass. In some cardiac surgical cases, we cool the body temperature very low even down to 18°C for organ protection during cardiopulmonary bypass. Because solubility of isoflurane goes up significantly at this extreme cold temperature, I was curious what isoflurane could do to the body in this circumstance. Although the anaesthetic mechanism of volatile anaesthetics remains to be elucidated, these small molecules were proposed to be promiscuous (have multiple binding sites). One of the significant complications is perioperative infection in this population, and I wanted to see if they would affect immune cells as well by directly affecting some proteins.

Dr Yuki and his team at Boston Children's Hospital. Dr Yuki (on the left) and his team (from left to right) Wei Wang, Matt Chamberlain, Sophia Koutsogiannaki, Hui Zha, Kazumasa Tawaza and Erika Matsunami

What are the implications of your research for the clinical usage of anaesthetics?
So far our research is based on animal model experiments. In our model, volatile anaesthetic(s) may not be favourable in the setting of severe sepsis, but various reports suggest that volatile anaesthetics may be favourable in a systemic inflammatory state without infection. We need to elucidate the role of different anaesthetics in various contexts and also we need to validate our findings in patients. This will be an exciting field to study.

Where do you hope your research will go from here?
We still do not know how anaesthetics cause anaesthesia. How these small molecules work and where they target in the central nervous system is being actively studied. Understanding immunological targets of current anaesthetics and clinical consequences can allow clinicians to think when and which anaesthetics should be used in a certain context. However, there may be a situation when current anaesthetics are not favourable. Understanding these anaesthetic and immunological mechanisms of current anaesthetics will eventually allow us to develop new anaesthetics devoid of immunological effects.

How important has collaboration been for your research so far?
Collaborations have been very helpful for me to facilitate our research. They not only provide us with great research tools but also give us great scientific feedback. In addition, meeting with well-established scientists in the field is a very special experience for me, and it has been a great learning process. I am sincerely thankful for all the people who have helped me throughout this process. This would have never been possible without the support that I have received from my family, mentors and colleagues.

Are there indications that anaesthetics affect other processes in the human body besides immune function?
Yes, I think so. For example, some anaesthetics affect the cardiovascular system as well. As a clinician who anaesthetises critically-ill children with congenital heart diseases, cardiovascular effects of anaesthetics are important issues to consider. By identifying these targets that potentially worsen cardiovascular physiology, we might be able to develop anaesthetics devoid of cardiovascular effects as well.

Detail

RESEARCH OBJECTIVES

Dr Yuki's laboratory research focuses on determining the pathophysiology behind sepsis and understanding the impact of anaesthetics on immune function during surgical operations.

FUNDING

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COLLABORATORS

- Timothy Springer, PhD (Boston Children's Hospital)
- Sulpicio Soriano, MD (Boston Children's Hospital)
- Charles Serhan, PhD (Brigham and Women's Hospital)
- Jean Lee, PhD (Brigham and Women's Hospital)
- Roderic G Eckenhoff, MD (University of Pennsylvania)
- Takehiko Yokomizo, MD, PhD (Juntendo University, Japan)

BIO

Dr Yuki obtained his MD from the University of Tokyo. After his initial medical training in Japan, he moved to the USA to complete a surgical internship at the University of Hawaii, an anaesthesia residency in Massachusetts General Hospital, and fellowships in paediatric anaesthesia and paediatric cardiac anaesthesia at Boston Children's Hospital.

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