Received: 1 October 2019 | Revised: 9 October 2019 | Accepted: 10 October 2019

DOI: 10.1111/bph.14908

COMMENTARY

1 + 1 = 4? Balanced anaesthesia: A sum that is greater than its parts

Yingqiu Zhou[1,2] | David M. Roth[1,2] | Hemal H. Patel[1,2]

[1]Research Services, Veterans Administration San Diego Healthcare System, San Diego, California

[2]Department of Anesthesiology, UCSD School of Medicine, San Diego, California

Correspondence
Hemal H. Patel, PhD, Department of Anesthesiology, UCSD School of Medicine, 9500 Gilman Drive, San Diego, CA.
Email: hepatel@ucsd.edu

Funding information
U.S. Department of Veterans Affairs, Grant/Award Number: BX001963; National Institutes of Health, Grant/Award Numbers: AG052722 and HL091071

Anaesthetics are one of the most widely used pharmacological agents today, but the field of anaesthesiology is quite young. A reversible state of amnesia, analgesia, immobility, and unconsciousness characterizes the general premise of anaesthesia. Before 1846, there was a lack of agents that rendered procedures completely pain free; therefore, procedures were "quick and dirty." This is in contrast to procedures performed today: slow, controlled, and methodical. William Morton discovered that inhalation of ether rendered his patients unconscious and free of pain for dental procedures. Subsequently, ether was used successfully to induce general anaesthesia in a public demonstration for a neck tumour removal. Other anaesthetics with improved properties quickly followed that did not have ether's unwanted flammable and explosive properties. Booth and Bixby in 1932 recognized that fluorine substitutions would be necessary for developing a non-combustible anaesthetic, and many agents were synthesized, although only a few became widely used. **Halothane** was synthesized by Charles Suckling in 1954 and used in standard clinical practice worldwide until it was stigmatized by reports of post-operative liver failure. Despite studies that showed the contrary, the link between halothane and hepatitis remained. Other fluorinated volatile anaesthetics without significant side effects were synthesized in the 1960s–1970s. **Isoflurane**, **sevoflurane**, and **desflurane**, three of the volatile anaesthetics synthesized at that time, are still in clinical use today (Denomme, Hull, & Mashour, 2019).

Ultimately, a search ensued for potential intravenous anaesthetics to avoid the unpleasantness of the inhalation of vapours. The first successful instance of intravenous anaesthesia occurred in 1872 when Pierre-Cyprien Oré administered chloral hydrate to his patients. **Sodium thiopental**, a barbiturate and **GABA** agonist, became popular after John Lundy's detailed description popularized it. More importantly, Lundy also introduced the concept of "balanced anaesthesia" in 1926, in which a combination of agents is used to achieve the desired anaesthetic effect with fewer side effects—a concept that remains a goal of modern anaesthesia practice. In this edition of the *BJP*, Kent, Savechenkov, Bruzik, and Miller (2019) add important data regarding the additivity and/or synergy of **$GABA_A$ receptor** agonists used in combination. The novel finding that the structural pharmacology of GABA agonists could predict the additive or synergistic anaesthetic effects in vivo has important implications towards modern anaesthetic practice.

Historically, the term "anaesthesia" was introduced (*Greek: lacking sensation*) in the same year as general anaesthesia was first publicly performed in 1846 as a *physiological* change brought on by ether. John Snow led the pharmacological investigation of anaesthetics and studied scientific principles to guide anaesthetic administration. He designed devices that allowed for controlled delivery of ether and **chloroform**. John Snow also demonstrated that engineered vaporizers delivered safer anaesthetics compared to saturated cloths—emphasizing the importance of understanding pharmacological principles to reduce morbidity and mortality. Despite a historical focus on the physiological changes and pharmacological principles involved in the anaesthetic state, the mechanisms of action of anaesthetic agents are still unclear.

Our knowledge of anatomical and molecular targets has, however, grown over time. The inhalational potency of widely different groups of anaesthetic agents was shown to correlate with lipid solubility. This finding led to the well-known theory developed independently by Meyer and Overton at the turn of the 20th century, which postulated that anaesthetics act on bulk lipid membranes. As further studies were conducted, this mechanism seemed less likely as the change in lipid fluidity produced by anaesthetics was only observed at concentrations much higher than concentrations needed for surgical anaesthesia. The Meyer and Overton hypothesis also applied only to

inhalational anaesthetics and was complicated by IV anaesthetics. Later, studies on anaesthetic–protein interactions gained traction. A turning point in the general acceptance of the importance of anaesthetic–protein interactions occurred in 1984 when a study by Franks and Lieb showed that firefly luciferase activity is competitively inhibited by 50% at concentrations of anaesthetic identical to those used to anaesthetize animals (Franks & Lieb, 1984). Since then, studies have shown anaesthetic interactions with other proteins, including interactions with voltage-gated and ligand-gated ion channels (Franks & Lieb, 1994).

The $GABA_A$ receptor, an ionotropic and ligand-gated receptor, has been widely studied as a site of action of a wide range of general anaesthetics. $GABA_A$ receptors are one of the most abundant inhibitory neurotransmitter receptors in the CNS. Thus far, there are at least 19 genes identified that code for $GABA_A$ receptor subunits, and different regions in the brain express at least nine subunit configurations, each with different pharmacological properties. As such, it makes sense that $GABA_A$ receptors are involved in higher order brain functions such as awareness, consciousness, and memory (Garcia, Kolesky, & Jenkins, 2010). The current paper by Kent et al. furthers our understanding of the precise mechanism and behaviour of anaesthetics on $GABA_A$ receptors. Previous work has shown that diverse types of general anaesthetics - gaseous, volatile, and intravenous - all interact with $GABA_A$ receptors to enhance inhibitory currents. Furthermore, these interactions were shown to be additive or, in limited experiments in mammals, synergistic between two types of agents (Cao et al., 2018). Using tadpoles as a simple model to remove uncertainties that come with the complex pharmacokinetics in mammals, the current study demonstrates that anaesthetic potencies of agents which bind to one of three classes of general anaesthetic sites on synaptic $GABA_A$ receptors are additive, whereas those that bind to different sites are synergistic. Moreover, the strength of the synergy increases with involvement of more binding sites.

We have sought to develop anaesthetics with minimal off-site target effects, and thus clinical side effects, ever since ether was used in 1846. The current study provides another stepping stone towards our understanding of anaesthetic mechanisms and perhaps further study into the development of anaesthetics that act allosterically to avoid unwanted clinical side effects—or in a broader sense, continue the study and development of anaesthetics keeping the concept of "balanced anaesthesia" in mind.

Limitations of the study include unknown possible complications in mammals given more complex protein interactions and rapid diffusion of intravenous anaesthetics away from sites of action, as well as the empirical finding that widely clinically used anaesthetics have less site specificity than the agents used in the study. The message, however, that is reminiscent of Lundy's concept over 90 years ago that anaesthesiologists today observe, still stands—as drugs evolve and our understanding of physiological effects broaden, the idea of using anaesthetics that act at multiple sites to achieve intended effect with as little side effects as possible is still relevant. Today, rarely is a single drug used as a general anaesthetic. The concept of using a combination of different forms of anaesthesia, including regional anaesthesia, and the concept of multimodal pain management support this critical concept. The synergistic effect of drugs that bind to different sites on the $GABA_A$ receptor serves as a reminder that we should continue to investigate the mechanisms of action of anaesthetics. With a better understanding of the mechanism(s) of action of anaesthetics, we can significantly improve outcomes for patients, facilitate the development of more efficacious and safer drugs, develop improved anaesthetic practice, and better understand the neurological mechanisms that underlie the nervous system functions, such as consciousness and memory.

ACKNOWLEDGEMENTS

Funding was partly provided by the National Institutes of Health (Grants HL091071 and AG052722) and the U.S. Department of Veterans Affairs (Grant BX001963) to H.H.P.

CONFLICT OF INTEREST

H.H.P. has equity as a founder in CavoGene LifeSciences Holdings, LLC.

ORCID

Hemal H. Patel https://orcid.org/0000-0001-6722-9625

REFERENCES

Cao, L. Q., Montana, M. C., Germann, A. L., Shin, D. J., Chakrabarti, S., Mennerick, S., … Akk, G. (2018). Enhanced GABAergic actions resulting from the coapplication of the steroid 3α-hydroxy-5α-pregnane-11,20-dione (alfaxalone) with propofol or diazepam. *Scientific Reports*, *8*, 1–12. https://doi.org/10.1038/s41598-018-28754-7

Denomme, N., Hull, J. M., & Mashour, G. A. (2019). Role of voltage-gated sodium channels in the mechanism of ether-induced unconsciousness. *Pharmacological Reviews*, *71*, 450–466. https://doi.org/10.1124/pr.118.016592

Franks, N. P., & Lieb, W. R. (1984). Do general anaesthetics act by competitive binding to specific receptors? *Nature*, *310*, 599–601. https://doi.org/10.1038/310599a0

Franks, N. P., & Lieb, W. R. (1994). Molecular and cellular mechanisms of general anaesthesia. *Nature*, *367*, 607–614. https://doi.org/10.1038/367607a0

Garcia, P. S., Kolesky, S. E., & Jenkins, A. (2010). General anesthetic actions on GABA(A) receptors. *Current Neuropharmacology*, *8*, 2–9. https://doi.org/10.2174/157015910790909502

Kent, D. E., Savechenkov, P. Y., Bruzik, K. S., & Miller, K. W. (2019). Binding site location on $GABA_A$ receptors determines whether mixtures of intravenous general anesthetics interact synergistically or additively *in vivo*. *British Journal Pharmacology*, 1–13. https://doi.org/10.1111/bph.14843