Song
Anesthesiology and Perioperative Science (2024) 2:4
https://doi.org/10.1007/s44254-023-00040-4

Anesthesiology and Perioperative Science

RESEARCH HIGHLIGHTS

Open Access

The role of KCC2 in recovery of consciousness from anesthesia

Xue-Jun Song[1,2*]

Keywords Consciousness, General anesthesia, Emergence, VPM, KCC2, GABA

General anesthesia can cause reversible loss of consciousness (LOC). Since the first application of general anesthetics in the 1840s, the anesthetic-induced reversible LOC has been used as a biomedical model for studying loss and regain of consciousness [1]. There have been several hypotheses on how the anesthesia could be induced by the diverse anesthetics [2–4]. However, we still know little about how the brain emerges from anesthesia. A recent study by Hu et al. [5] provides a novel neuronal and molecular mechanism of ubiquitin-proteasomal degradation of K^+/Cl^- cotransporter 2 (KCC2) in the ventral posteromedial nucleus (VPM) of the thalamus by which the brain emerges from anesthesia and to regain consciousness.

The study by Hu et al. [5] demonstrates that the downregulation of KCC2 occurs rapidly when the brain is forced, by diverse anesthetics, into a minimally responsive state (MRS). The expression of KCC2 in the VPM maintains at the minimum low level during the MRS and recovers after the brain exits from the MRS. Such a downregulation of KCC2 leads to γ-aminobutyric acid type A receptor ($GABA_AR$)-mediated disinhibition, enabling accelerated recovery of VPM neuron excitability and emergence of consciousness from anesthetic inhibition (see Fig. 1). The authors first screened the whole brain including the eight brain regions and seven subnuclei of the thalamus and hypothalamus and finally identified the VPM as the relevant nucleus, where the downregulation of KCC2 orchestrates the emergence of consciousness. There is a precise projection from the VPM to the cortex of the postcentral somatosensory area and a long-standing hypothesis that the thalamocortical feedback loop is crucial for conscious perception. In this study, the authors proposed that the VPM is the key nucleus in the thalamocortical signal transmission and cortical activation and that KCC2 downregulation-mediated disinhibition of the VPM neurons may be one of the most important mechanisms driving neural functional network reconstruction from anesthesia disruption.

The recovery of consciousness from anesthesia was once assumed to be a passive process, spontaneously occurring as residual levels of anesthetics dwindle below a critical value due to gradual elimination of the anesthetic from the body. Recently, it is demonstrated that emergence from anesthesia is controllable by manipulating certain neurotransmitter systems, including acetylcholine, norepinephrine, orexin/hypocretin, dopamine and adenosine, in different brain nuclei might accompany or be related to the process of emergence from anesthesia [6, 7]. In the study by Hu et al.[5], it is elucidated, for the first time, that the re-emergence of consciousness is an active process, which is orchestrated by the intrinsic ability of the brain. Of course, if an anesthetic sustained at high enough concentrations, the intrinsic driving force of the brain would not be able to successfully restore the anesthetic inhibition. The ubiquitin-proteasomal degradation of KCC2 in the VPM serves as the mechanism by

*Correspondence:
Xue-Jun Song
songxuejun@sustech.edu.cn
[1] Department of Medical Neuroscience, School of Medicine, Southern University of Science and Technology, Shenzhen 518055, China
[2] SUSTech Center for Pain Medicine, Southern University of Science and Technology, Shenzhen 518055, China

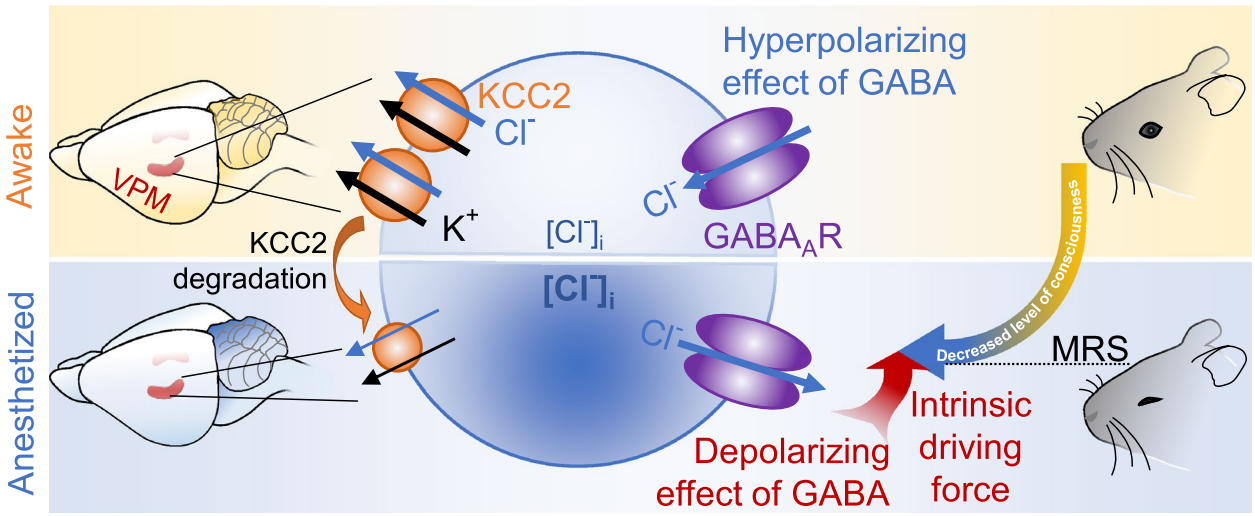

Fig. 1 Schematic diagram of KCC2 degradation promoting recovery of consciousness from general anesthesia. When the brain is forced, by diverse anesthetics, into a MRS, the expression of KCC2 in the VPM decreases and maintains at the minimum low level during the MRS and recovers after the brain exits from the MRS. Such a downregulation of KCC2 leads to γ-aminobutyric acid type A receptor ($GABA_AR$)-mediated disinhibition, enabling accelerated recovery of VPM neuron excitability and emergence of consciousness from anesthetic inhibition

which the brain emerges from anesthesia to regain consciousness. KCC2 downregulation is driven by ubiquitin ligase Fbxl4. Phosphorylation of KCC2 at Thr1007 promotes interaction between KCC2 and Fbxl4. These findings support an idea that, when the brain is forced to the verge of MRS, the brain initiates a KCC2 degradation program to resist the sharply sustained decreasing of consciousness level into the MRS and to regain consciousness from anesthetic inhibition [5].

The authors also demonstrate that the ubiquitin degradation of KCC2 may serve as a common molecular mechanism for the active reboot of consciousness and is independent of anesthetic choice. Four different anesthetics including the propofol, pentobarbitone, ketamine, and isoflurane were used in the study by Hu et al. These anesthetics have different pharmacological properties and share the same or different molecular targets. Although we have considered that ketamine produces anesthesia by acting on the N-methyl-D-aspartic acid receptors (NMDAR), and that propofol, pentobarbital and isoflurane produce anesthesia by acting on $GABA_AR$ [2–4], this study shows that these anesthetics may induce KCC2-Thr1007 phosphorylation, a key for the ubiquitin degradation of KCC2, through NMDAR- and $GABA_AR$-independent pathways [5].

Finally, we know that many clinical reports describing epileptic seizures occurring during anesthesia. Interestingly, it is also reported in this study [5] in the anesthetized mice, which exhibited sustained seizure-like tremors, typically during the period of exiting from the MRS and before the recovery of consciousness. The authors speculate that the ubiquitin degradation of KCC2 and the subsequent events may be responsible for such anesthetic epilepsy.

Abbreviations

LOC	Loss of consciousness
KCC2	K^+/Cl^- cotransporter 2
VPM	The ventral posteromedial nucleus of the thalamus
MRS	Minimally responsive state
$GABA_AR$	γ-Aminobutyric acid type A receptors
NMDAR	N-methyl-D-aspartic acid receptors

Acknowledgements
Not applicable.

Authors' contributions
The author read and approved the final manuscript.

Funding
The work is supported by The National Natural Science Foundation of China (grant no. NSFC82350710225).

Competing interests
The author declares no conflict of interests.

Received: 25 May 2023 Revised: 15 October 2023 Accepted: 5 November 2023
Published online: 02 January 2024

References

1. Miller KW. Anaesthesia: Models of consciousness. Nature. 1986;323(6089):584. https://doi.org/10.1038/323584a0.
2. Rudolph U, Antkowiak B. Molecular and neuronal substrates for general anaesthetics. Nat Rev Neurosci. 2004;5(9):709–20. https://doi.org/10.1038/nr1496.

3. Hemmings HC Jr, Riegelhaupt PM, Kelz MB, Solt K, Eckenhoff RG, Orser BA, et al. Towards a Comprehensive Understanding of Anesthetic Mechanisms of Action: A Decade of Discovery. Trends Pharmacol Sci. 2019;40(7):464-81. https://doi.org/10.1016/j.tips.2019.05.001.
4. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. Science. 2008;322(5903):876–80. https://doi.org/10.1126/science.1149213.
5. Hu JJ, Liu Y, Yao H, Cao B, Liao H, Yang R, et al. Emergence of consciousness from anesthesia through ubiquitin degradation of KCC2 in the ventral posteromedial nucleus of the thalamus. Nat Neurosci. 2023;26(5):751–64. https://doi.org/10.1038/s41593-023-01290-y.
6. Curtis D, Stevens WC. Recovery from general anesthesia. Int Anesthesiol Clin. 1991;29(2):1–11. https://doi.org/10.1097/00004311-199121000-00003.
7. Kelz MB, García PS, Mashour GA, Solt K. Escape From Oblivion: Neural Mechanisms of Emergence From General Anesthesia. Anesth Analg. 2019;128(4):726–36. https://doi.org/10.1213/ANE.0000000000004006.

Publisher's Note