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γ-Aminobutyric Acid-Mediated Neurotransmission Inhibition in the Pontine Reticular Formation: A Potential Mechanism of Propofol Anesthesia

Mary K. Pathak,* Senzhu Bao,† Fred Wang *,Δ

Study for underlying anesthetic mechanisms is the key point of general anesthesia. Propofol is a representative of general anesthetics. Many general anesthetics are thought to produce a loss of wakefulness, in part, by enhancing *γ*-aminobutyric acid (GABA) neurotransmission. However, GABAergic neurotransmission in the pontine reticular formation promotes wakefulness. We hypothesized that propofol inhibited GABA current and promoted long-term potentiation (LTP) of pontine tissue, which might be the underlying mechanism of propofol anesthesia. In our pre-study investigation, propofol enhanced GABA current in the thalamic neuron and showed as a characteristic of burst discharge, but burst inhibition was observed in the pontine neuron. Hence, the hypothesis of the GABAergic neurotransmission inhibition in the pontine reticular formation might be the mechanistic base of propofol anesthesia, and given an experimental basis of the theory of central nervous inhibition in general anesthesia.■

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BIG ADVANCE has being made in exploring the pharmacological mechanisms of general anesthesia since the first case reported anesthetized with ether in 1846, but the precise recognition of the mechanism is still unclear because of the complexity of the nervous system. Approximately 160 million patients underwent general anesthesia every year in the world, and the mortality associated with general anesthesia was near one per ten thousands (1), and the incidence of related complications including recognition dysfunction and hypomnesis was up to 30 per cent (2). These high incidences of complications and mortality are attributed to inadequate knowledge of the potential mechanisms of general anesthesia (3). As thus it is one of the challenges for clarifying the underlying mechanisms of general anesthetics to anesthetic professionals.

To date, several theories produced on the pharmacological mechanisms of general anesthetics, such as activation or inhibition of the ion channels, receptor regulation of neuron synapse, involvement of neurotransmitter receptors and the balancing regulation of excitatory and inhibitory networks of the nervous system (3). Each theory has its own basis, but it alone cannot explain the complexity of the general anesthesia in whole. Therefore, there have potentially pivotal implications in identifying the mechanisms of general anesthetics' neurobehavioral effectiveness.

Hypothesis

Components of the anesthetized state include unconsciousness, immobility, sedation, amnesia and analgesia (4), and the unconscious state is produced through enhancing GABAergic neurotransmission by the general anesthetics (5). This gives a hint that the activation of the GABAergic nervous network plays an essential role in the anesthetizing effectiveness of general anesthesia. Besides, this also is the base of the theory of central inhibition of general anesthesia (6). The ascending reticular activating system (ARAS) plays a key role in wakefulness, in which the pontine reticular formation is the major part functioning through GABAergic neurotransmission. Interestingly, however, the recognition of the conception of the pontine reticular formation's role in wakefulness by activating the GABAergic network (7) is contrasting with the knowledge of the general anesthetics, which reaches unconsciousness by enhancing GABAergic neurotransmission. As thus we hypothesized that the general anesthetics produced loss of consciousness by inhibiting GABAergic neurotransmission of the pontine reticular formation. Therefore, it would provide an experimentally novel basis for the effect of general anesthetics if the detailed role for GABAergic neurotransmission of pontine reticular formation was clarified during general anesthesia.

So far, general anesthetic was mainly divided into two kinds of, i.e. intravenous and inhalable anesthetics, and propofol is the representative of intravenous general anesthetic. Previous study has showed that propofol produced unconsciousness through regulating GABAergic neurotransmission of hypothalamic sleeping pathways (5). Meanwhile, mutative research discovered that propofol and sevoflurane displayed the nerve-inhibiting effect via different binding sites on neuron, but this originally separated inhibition was integrated by affecting the activity of GABA receptor (8). Moreover, different anesthetics produce similar anesthetic effectiveness showed that a common pathway might exist. Exploring and verifying such potentially common binding sites has a clinically important implication. Above mentioned common functioning pathway theory was consistent with our presumption whether the GABAergic neurotransmission in pontine reticular formation functioning as the molecular basis of wakefulness was inhibited or not during propofol anesthesia, and it played the role of information integration in general anesthesia or not are yet to be guaranteed in the further studies.

To verify the role for GABAergic neurotransmission inhibition in the pontine reticular formation during general anesthesia, a pre-study investigation was performed. We recorded the whole-cell GABA current of hippocampal neuron, nucleusdorsomedialthalamus neuron and pontine neuron with voltage patch clamp during propofol incubation, and found that propofol played a significant role in enhancing GABA current in nucleusdorsomedialthalamus neuron, and minor effect on hippocampal neuron, but all two kinds of neuron displayed a characteristic of burst discharge. However, burst inhibition was observed in pontine neuron after propofol treatment (see Fig. 1). These results were consistent with previous reports regarding the role

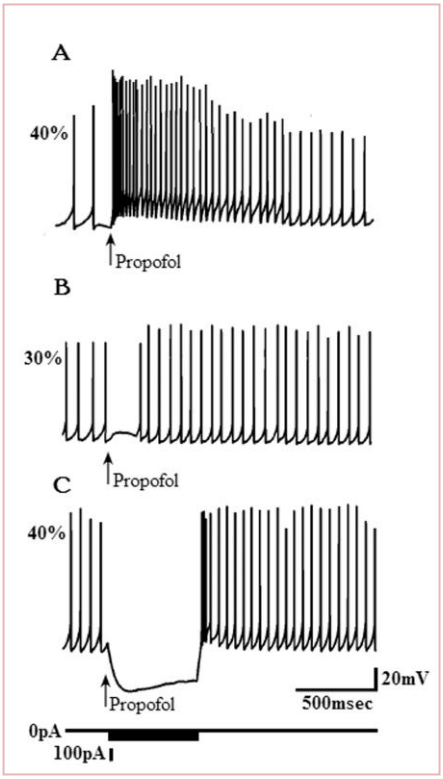

Figure 1. Effect of propofol on GABAergic current in different neurons.

The whole-cell GABA current of hippocampal neuron, nucleus dorsomedial thalamus neuron and pontine neuron with voltage patch clamp were recorded during propofol incubation. Propofol played a significant role in enhancing GABA current in nucleus dorsomedial thalamus neuron (Panel A), and minor effect on hippocampal neuron (Panel B), but all two kinds of neuron displayed a characteristic of burst discharge. However, burst inhibition was observed in pontine neuron after propofol treatment (Panel C).

for propofol in hypothalamus and hippocampus (5, 9). Based on this observation, a standardized current curve of pontine tissue section stimulated with GABA was built up (data were not shown), and then incubated with propofol for measuring the long-term depression (LTD) as the symbol of central inhibition during general anesthesia (10), which was for investigating the potential relationship between GABA inhibition and LTD. We found that propofol significantly inhibited pontine GABA current, but increased LTD (see Fig. 2). As thus we hypothesized that GABA-mediated neurotransmission inhibition in pontine reticular formation played a crucial role in the loss of consciousness during propopfol anesthesia.

Methodology of Testing the Hypothesis

To verify this hypothesis and find novel mechanism of general anesthesia, following procedures should be performed on the basis of the pre-study investigation. First, the induction time of propofol anesthetized cat will be recorded and the GABA level in the pontine reticular formation will be simultaneously measured with microdialysis technique, and their potential relationship will be analyzed. Furthermore, GABA absorbing inhibitor nipecotic acid (NCA) or GABA synthetic inhibitor 3-Mercaptopropionic acid (3-MPA) will be injected into the pontine reticular formation of cat using the intracranial microinjection technique, and then will make following detections: 1) record propofol induction time and respiratory rate, and compare the GABA levels after the two GABA inhibitors administration; 2) compare the difference of resuscitation time after propofol anesthesia and the GABA levels in the pontine reticular formation during the resuscitating period; 3) a polygraphic system can be used to record the cortical electroencephalogram and neck muscle electromyogram as the signals to assess arousal state, and observe the influence of propofol on GABAergic neurotransmission in the pontine reticular formation; 4) the expression of glutamate receptor-interacting protein (GRIP) (11) and transmembrane AMPA receptor regulatory protein γ2 (TARP γ2) (12) will be detected as the symbol of LTD. In addition, GABA current and LTD will be recorded with tissue electrophysiology after incubating pontine tissue section and cultured neuron. After then administered NCA or 3-MPA to observe the effect of propofol on GABA current.

Concluding Remarks

In conclusion, GABAergic neurotransmission inhibition in the pontine reticular formation might be an underlying mechanism of general anesthesia. This hypothesis should be verified by investigating the relationship among the propofol induction time, pontine GABA level, cortical electroencephalogram and

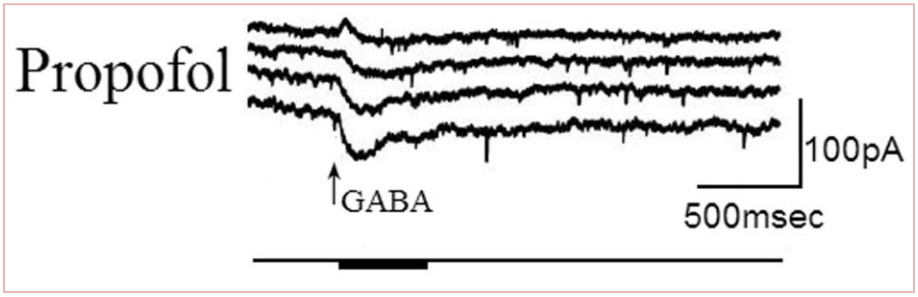

Figure 2. Effect of propofol on GABAergic current and long-term depression of pontine section.

Pontine tissue section was incubated with propofol for measuring the long-term depression (LTD). Propofol significantly inhibited pontine GABA current.

neck muscle electromyogram after injection of GABA absorbing inhibitor and synthetic inhibitor into pontine reticular formation through intracranial microinjection in propofol anesthesia. Furthermore, the influence of propofol on GABA level and LTD of pontine tissue section should be explored to unravel the underlying mechanism of propofol anesthesia. To date, given the precise role for GABAergic neurotransmission in the pontine reticular formation during propofol anesthesia, to our knowledge, is unknown, as thus this study possesses the originality.■

Conflict of Interest

None

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