B-14 (23-8) Pharmacological Effects of General Anesthetics Altered by the Change of Subunit Composition of GABAA Receptors

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BACKGROUND : GABAA receptor is the main inhibitory receptor in the central nervous system and is molecular target of many general anesthetics. GABAA receptors comprise a heteropentameric protein complex assembled from 16 different subunits. The subunit constitution determines the pharmacological properties of the GABAA receptors. Therefore, genetically modified animals in a molecule related to the GABAergic neurotransmission exhibit different pharmacological responses to the anesthetic drugs. We have clarified that phospholipase C-related but catalytically inactive protein (PRIP) plays important roles in the intracellular transport of GABAA receptors.

OBJECTIVES : In this study, we investigated the pharmacological responses of anesthetic drugs in *Prip*-KO mice.

MATERIALS & METHODS : We homogenized the whole brain of *Prip*-KO and wild-type mice and fractionated into whole tissue fraction and plasma membrane fraction by centrifugation method. The expression of each subunit of GABAA and NMDA receptors in those fractions was analyzed by immunoblotting using each specific antibody. Propofol, etomidate, pentobarbital, and ketamine were intraperitoneally injected into *Prip*-KO and wild-type mice, and onset and duration time of loss-of-righting reflex were analyzed. Furthermore, mice were implanted with electroencephalogram and electromyogram electrodes for polysomnographic recordings. After recovery period, the mice were performed the polysomnography by administration of propofol and pentobarbital, and sleep-wake stages were analyzed.

RESULTS : Immunoblot analyses showed that the expression of β3 subunit of GABAA receptors was specifically decreased in the plasma membrane fractions of *Prip*-KO mice. Propofol- and etomidate-induced hypnosis were significantly decreased in *Prip*-KO mice, and sleep time measured by polysomnographic recordings was dramatically reduced in *Prip*-KO mice by administration of propofol.

CONCLUSION : Since the cell surface expression of β3 subunit of GABAA receptors was significantly reduced in *Prip*-KO mice compared with wild-type mice, the pharmacological effects of propofol and etomidate was significantly attenuated in *Prip*-KO mice. Therefore, PRIP may regulate the intracellular trafficking of GABAA receptor β subunit.