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

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BACKGROUND : GABA$_A$ receptor is the main inhibitory target of many general anesthetics. GABA$_A$ receptors comprise a heteropentameric protein complex assembled from a total of 19 different subunits. The molecular mechanisms underlying the pharmacological properties of the GABA$_A$ receptors. Therefore, genetically modified animals in a molecule related to the GABAergic neurotransmission exhibit different pharmacological responses to their drugs. We have clarified that phospholipase C-related cell but catalytically inactive protein (PRIP) plays important roles in the intracellular transport of GABA$_A$ 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 GABA$_A$ 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 [illegible] righting reflex were analyzed. Furthermore, mice were implanted with electroencephalogram and electromyogram electrodes under pentobarbital anesthesia. After a recovery period, the mice were performed the polysomnography by administration of propofol and pentobarbital, and sleep-wake stages were analyzed.

RESULT : Immunoblot analysis revealed that the expression of β3 subunit of GABA$_A$ 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 GABA$_A$ 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 GABA$_A$ receptor β subunit.