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Disrupting N-methyl-d-aspartate receptor-postsynaptic density protein-95 interactions reduces the threshold for halothane anesthesia

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Abstract

Our previous studies have shown that clinically relevant concentrations of inhalational anesthetics dose-dependently and specifically inhibit the PSD-95, Dlg, and ZO-1 (PDZ) domain-mediated protein interactions between postsynaptic density protein 95 (PSD-95) and N-methyl-d-aspartate (NMDA) receptors, and that the knockdown of spinal PSD-95 by intrathecal injection of PSD-95 antisense oligodeoxynucleotide significantly reduces the minimum alveolar anesthetic concentration (MAC) for isoflurane. In this study, we constructed a fusion peptide, Tat-PSD-95 PDZ2, comprising the second PDZ domain of PSD-95, which can specifically disrupt PSD-95 PDZ2-mediated protein interactions by binding to its interaction partner. By intraperitoneal injection of this fusion peptide, we investigated the effect of disrupting the PSD-95 PDZ2-mediated protein interactions on the threshold for halothane anesthesia. We found that systemically injected cell-permeant fusion peptide Tat-PSD-95 PDZ2 was delivered into the central nervous system, disrupted the protein-protein interactions between NMDA receptor NR2 subunits and PSD-95, and significantly reduced the MAC and righting reflex EC50 for halothane. These results suggest that PDZ domain-mediated protein interactions at synapses in the central nervous system might play an important role in the molecular mechanisms of halothane anesthesia.

Biography

Feng Tao is an Assistant Professor in the Department of Anesthesiology and Critical Care Medicine at Johns Hopkins University School of Medicine. Dr. Tao received his research support from Maryland Stem Cell Research Fund, the Blaustein Pain Research Fund, and NIH RO1 grant. He has published 30 papers in peer-reviewed professional journals and he is serving as an editorial board member for several professional journals. Dr. Tao also served as an invited reviewer for Johns Hopkins ACCM Seed Grant, NSF-sponsored Pilot Funding at Louisiana State University, and Wings for Life–Spinal Cord Research Foundation in Austria.