International Congress Series 1283 (2005) 9–14

www.ics-elsevier.com

Significances of protein structure and dynamics in anesthetic action

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Abstract. The structure–function paradigm emphasizes the importance of structural changes in mediating protein functions. Can this paradigm ultimately offer a mechanistic understanding of the action of general anesthetics? We have combined structural and dynamical studies, both experimentally and computationally, to determine the effects of general anesthetics on the structures and dynamics of a broad range of proteins, including neuronal nicotinic acetylcholine receptors (nAChRs) and glycine receptors (GlyRs) that have been recognized as the potential physiological targets for general anesthetics, and other model proteins, such as gramicidin A channel, whose structures have been well resolved. We have attempted to relate the detailed changes in the structures and dynamics of these proteins to the possible functional consequences upon interaction with volatile anesthetics. Our results discount the importance of structural fitting between anesthetic molecules and the "protein pockets", and underscore the anesthetic effects on protein global dynamics in producing functional change in proteins. © 2005 Published by Elsevier B.V.

Keywords: Glycine receptors; Acetylcholine receptors; Mechanisms of general anesthesia; Protein dynamics

1. Introduction

Although it is still debatable whether proteins are solely responsible for mediating general anesthetic actions or perhaps lipids also play certain roles, it is generally agreed that proteins, especially postsynaptic neurotransmitter-gated ion channels, are targeted and modulated by general anesthetics. Along with the advancement in the structure determination of complex

Abbreviations: GlyRs, glycine receptors; nAChRs, nicotinic acetylcholine receptors; gA, gramicidin A; DPC, dodecylphosphocholine; GST, glutathione S-transferase; NMR, nuclear magnetic resonance; TM2, TM3, TM23, second, third, and second+third transmembrane domain.

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0531-5131/ © 2005 Published by Elsevier B.V.
doi:10.1016/j.ics.2005.07.069

proteins, we are close than ever to an in-depth understanding of the molecular mechanisms of general anesthesia. There are still, however, some very fundamental issues that beg further investigations. One of them, on which this review will focus, is the importance of changes in protein dynamics in response to anesthetic modulations. For years, anesthesia research has been carried out based on a structure–function paradigm. Efforts have been devoted to identifying discrete hydrophobic protein pockets that allow for structural fitting with anesthetic molecules. Upon anesthetic binding to these pockets, the protein structures are expected to change, thereby altering the protein function. This viewpoint, while validated in many biological processes involving high-affinity drug binding, seems inadequate to explain the action of general anesthetics. A paradigm shift seems inevitable. The dynamics–function relationship, which is much less recognized and appreciated, is the crucial element in anesthetic–protein interaction that deserves to be studied systematically.

1.1. Possible effects of general anesthetics on protein structures

Proteins control the functions of living systems. The 3D spatial arrangements of the amino acids in proteins are crucial for protein functions. Except for the primary structures defined by the protein sequences, general anesthetics, in principle, can affect the secondary, tertiary, and quaternary structures. What remains unclear is how strong the anesthetic effects can be at different structural levels and how these effects can be quantified. In most of the model protein systems studied so far, few showed significant changes in secondary structures in response to general anesthetics at pharmacologically relevant concentrations. Although possibility still exists that α helices or β sheets can be distorted by general anesthetics, many experimental and computational studies suggest that the secondary structures of proteins are not very sensitive to general anesthetics [1,2].

Diversity in protein functionalities resides largely in the tertiary and quaternary structures. Whereas tertiary structure is related to the topology and global folding of single polypeptide chain, quaternary structures define the spatial arrangement of multiple distinct subunits that form a functional complex. Direct measurements of anesthetic effects on tertiary and quaternary structures of proteins have been limited due largely to technical difficulties in detecting subtle changes caused by anesthetics. With rapid development in structural biology, particularly with new NMR methods for measuring global topology based on the orientation constraints from the residual dipole coupling [3,4], it is anticipated that more information will become available in the near future.

1.2. Potential effects of general anesthetics on protein dynamics

Proteins are dynamic in nature [5–7]. The conventional crystallographic view of structures is actually the time and space averages of the protein molecules. Most high-resolution structures or static views of proteins are determined at low temperatures and often represent the “ground states” of the conformational ensemble. At the physiological relevant temperature, proteins may exist in numerous different conformational sub-states, which are best described by an energy landscape. Protein motions span a wide range of time scales. Not all but only some of the motions are directly coupled to protein function.

Comparing with the effort devoted to searching for the anesthetic binding pockets in proteins, much less effort has been dedicated to characterizing anesthetic effects on protein dynamics. This is due to the lack of a theoretical framework in recognizing the importance of