Progress in Biophysics and Molecular Biology 114 (2014) 153–169

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

Asymmetric perturbations of signalling oligomers

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ARTICLE INFO

Article history:
Available online 17 March 2014

Keywords:
Symmetric protein oligomers
Asymmetric activation
Ion channels
Transporters
Biophysical structural techniques
Symmetry-asymmetry distinction

ABSTRACT

This review focuses on rapid and reversible noncovalent interactions for symmetric oligomers of signalling proteins. Symmetry mismatch, transient symmetry breaking and asymmetric perturbations via chemical (ligand binding) and physical (electric or mechanic) effects can initiate the signalling events. Advanced biophysical methods can reveal not only structural symmetries of stable membrane-bound signalling proteins but also asymmetric functional transition states. Relevant techniques amenable to distinguish between symmetric and asymmetric architectures are discussed including those with the capability of capturing low-populated transient conformational states. Typical examples of signalling proteins are overviewed for symmetry breaking in dimers (GPCRs, growth factor receptors, transcription factors); trimers (acid-sensing ion channels); tetramers (voltage-gated cation channels, ionotropic glutamate receptor, CNG and CHN channels); pentameric ligand-gated and mechanosensitive channels; higher order oligomers (gap junction channel, chaperonins, proteasome, virus capsid); as well as primary and secondary transporters. In conclusion, asymmetric perturbations seem to play important functional roles in a broad range of communicating networks.

Contents

Abbreviations: AA, alternating access; ABC, ATP-binding cassette; ASIC, acid-sensing ion channel; β_2AR, β_2-adrenergic receptor; BRET, bioluminescence resonance energy transfer; CAP, catabolite activator protein; CNG, cyclic nucleotide-gated; cryo-EC, cryo-electron crystallography; EC, extracellular; EM, electron microscopy; EGFR, epidermal growth factor receptor; EPR, electron paramagnetic resonance; FRET, fluorescence resonance energy transfer; FS, fluorescence spectroscopy; $GABA_AR$, A-type γ−aminobutyric acid receptor; GPCR, G protein-coupled receptor; IC, intracellular; iGluR, ionotropic glutamate receptor; MD, molecular dynamics; MS, mass spectroscopy; NB, nucleotide binding; NGF, nerve growth factor; NMR, nuclear magnetic resonance; pLGIC, pentameric ligand-gated ion channel; SANS, small-angle neutron scattering; SAXS, small-angle X-ray scattering; TM, transmembrane; XRC, X-ray crystallography.

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http://dx.doi.org/10.1016/j.pbiomolbio.2014.03.001
0079-6107/

1. Introduction

What is so special in symmetry? Human perception of symmetric objects and structures has subjective and holistic characteristics. Symmetry can be associated with harmony, pleasure, stability (Blundell and Srinivasan, 1996; Goodsell and Olson, 2000; Kojić-Prodić and Štefanić, 2010; Thompson, 1952). In contrast, symmetry violation and asymmetry might seem disharmonic, transient and instable. It reflects some kind of motion or change: (bio)chemical reactions, transition states, function, metamorphosis, development, even revolution. These associations might seem trivial, but they are far from evident, especially if the motions and changes are very short, slight and invisible. The contrast between symmetry and asymmetry is present throughout the Universe, from Big Bang down to particle physics (e.g. Higgs boson). How is this contrast manifested in life sciences?

The maintenance of living organisms and adaptation to environmental challenges involve signalling processes. Chemical communication, the interaction of chemical signals with signalling proteins elicit physiological responses. Recent biophysical methods have revealed that these physiological processes involve several weak, rapid, reversible, non-covalent interactions. The structural secret of life is thus wrapped in a versatile network of physicochemical interactions (Gong et al., 2009; Zhou and Gilson, 2009). This review is focused on non-covalent interactions of signalling proteins with a few coupled covalent biochemical changes.

Most signalling proteins have oligomeric quaternary structures. These proteins have presumably evolved via gene duplication, repetition and fusion of ancient peptide modules into homo-oligomers (Broom et al., 2012; Dayhoff et al., 2010; Kuriyan and Eisenberg, 2007). This is obviously a source of emerging structural symmetry (André et al., 2008; Lee and Blaber, 2011; Schulz, 2009). Some of the benefits of symmetric oligomers are greater biosynthetic and folding efficiency; amenability to cooperativity, allosteric regulation and adaptation; stability and reduced aggregation (André et al., 2008; Broom et al., 2012; Goodsell and Olson, 2000).

How do oligomeric proteins function concerning symmetry? Monod, Wyman and Changeux (Monod et al., 1965) introduced a concerted, symmetric model of allostery to interpret regulatory mechanisms of oligomeric enzymes. According to the MWC model, ligand-free homooligomers exist in equilibrium of different states; oligomeric structures are symmetric; protomer conformations change in a concerted way; ligand binding maintains the symmetric arrangement of protomers whereas it shifts the equilibrium of pre-existing oligomeric conformations. The MWC model was extended to the acetylcholine receptor and other signalling proteins (Changeux et al., 1984; Karlin, 1967). In contrast to the MWC model, Koshland, Némethy and Filmer (Koshland et al., 1966) introduced a sequential model. According to the KNF model, conformational changes of protomers are consecutive and asymmetric. Ligands bind sequentially with increasing affinity when the structure of a ligand and its binding site are accommodated to each other via induced fit. It should be noted that symmetry maintenance was a contradicting issue in the MWC and KNF models. The demonstration of rapid dynamics of conformational ensembles of proteins has then led to the reconciliation of MWC and KNF models. According to the recent dynamic model, ligands select from pre-existing conformational states of proteins and binding to the most suitable one shifts the equilibrium (Boehr et al., 2009; Smock and Gierasch, 2009; Tsai et al., 1999). However, the side chains of individual protomers are accommodated to ligand binding (KNF model). Thus, both conformational selection and induced fit play important roles in molecular recognition. These principles can gradually gain application not only in biotechnology but also in the pharmacological fine-tuning of signalling (Maksay, 2011).

Structural symmetry is also important in protein dynamics (Matsunaga et al., 2012; Swapna et al., 2012). Global symmetry is often associated with local binding asymmetry (Goodsell and Olson, 2000). Some specific requirements of signalling oligomers such as rapid and reversible action cannot be reconciled with high stability. They need dynamic flexibility; a trade-off between stability and evolvability; interface mutations for diversification and signalling selectivity (Tokuriki and Tawfik, 2009). Some symmetric signalling oligomers have been recently shown to function via asymmetric perturbation, transiently breaking symmetry (Mowrey et al., 2013; Maksay, 2013). Asymmetric transition states can be hopefully exploited in structure-based drug design (Brown, 2006; Lee and Craik, 2009).

The term symmetry will be primarily used here in a structural sense. However, there is a universal definition: symmetry means invariance to transformations. This maintenance of properties is similar to thermodynamic stability. Indeed, the oligomeric symmetries of signalling proteins contribute to structural stability.

The structural asymmetries discussed here should be distinguished from the functional and operational asymmetries of proteins. Functional asymmetry can be observed when identical domains perform distinct tasks: i) the zinc fingers of the Egr-1 transcription factor perform rapid scanning and stable recognition (Zandarashvili et al., 2012) and ii) histidine kinase receptor dimers possess either kinase or phosphatase activities (Moore and Hendrickson, 2012). Operational asymmetry arises when the symmetry of enzyme reaction cycles is broken, which can lead to evolutionary consequences (García-Bellido, 1996).

In the first part of the review we summarize some of the advanced biophysical methodologies which can be instrumental in revealing transient structural asymmetry in oligomeric proteins. In the second part, the structural (a)symmetry of signalling proteins will be overviewed according to the oligomerization state, structural family and function.

2. Methods to reveal structural symmetry and asymmetry of oligomeric proteins

2.1. X-ray crystallography

X-ray crystallography (XRC) has become the major method for high-resolution structure elucidation of proteins. Due to the obstacles of crystallization, the XRC structures of just the extracellular (EC) ligand-binding or intracellular (IC) functional coupling