A new trend in neuropharmacology: from the concept of allosteric interaction, the molecular dynamics of signal transduction to allosteric modulation of brain receptors and drug discovery.

Jean-Pierre Changeux, Institut Pasteur & Collège de France, Paris.

Classically, the field of drug therapy relied upon “the relationship betwen isosterism & competitive phenomena” (1). The new strategy proposed for drug design in neuropharmacology is based upon the concept of *allosteric interaction* (2) initially proposed to account for the inhibitory feedback mechanism mediated by bacterial regulatory enzymes. In contrast with the classical mechanism of competitive, steric, interaction between ligands for a common site, allosteric interactions take place between topographically distinct sites and are mediated by a discrete & reversible conformational change of the protein (2).

The concept was soon extended to membrane receptors for neurotransmitters (3) and shown to apply to the signal transduction process which, in the case of the nicotinic receptor for acetylcholine (nAChR), links the ACh binding site to the ion channel (4). Pharmacological effectors, referred to as *allosteric modulators*, such as Ca^{++} ions or ivermectin, were discovered that enhance the transduction process when they bind to sites distinct from the orthosteric ACh site and the ion channel (4,5). The recent X-ray structures, at atomic resolution (5,6), of the resting & active conformations of prokaryotic homologs of the nAChR and eukaryotic receptors including the nAChR itself, in combination with atomistic molecular dynamics simulations (5) reveal several distinct quaternary transitions in the transduction process with tertiary changes which profoundly modify the boundaries between subunits. These interfaces host orthosteric and allosteric modulatory sites which structural organization changes in the course of the transition. The model emerging from these studies has lead to the conception and development of several new pharmacological agents (7).

Such allosteric transitions mediate the modulation of brain circuits involved for instance in the dual action of nicotine both as a drug of abuse and as a cognitive enhancer. Alterations in the modulation of brain functions by neurotransmitter receptors may result in severe neuro-psychiatric pathologies including Schizophrenia (8) or Alzheimer diseases. Looking for chemical therapies against Autism, a strategy was further elaborated on the basis of brain genes expression data, using the concept of coherent-gene groups controlled by transcription factors (TFs), which resulted in the design of allosteric modulators targeted toward specific TFs expressed at critical periods of brain development (9). By capitalizing on the constantly developing structural information at high resolution, the aim is the design of orthosteric and allosteric modulators for ligand gated ion channels which are not only selective but also specific to their site on one conformation of the receptor over the others. The strategy has been termed *state-based pharmacology* which should lead to the rational design of pharmacological agents with a characteristic physiological action such as activators vs inhibitors vs desensitizers (10). Some of them might be relevant to COVID-19 (11). These developments pave the way to a new orientation of neuropharmacology.

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