Available online at www.sciencedirect.com
SCIENCE DIRECT
Biochemical Pharmacology 70 (2005) 1267–1276
Discussion
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

Allosteric modulation of ligand-gated ion channels

Ron C. Hogg [a,*], Bruno Buisson [b,1], Daniel Bertrand [a]

[a] Department of Neurosciences, Medical Faculty, CMU 1, rue Michel Servet, CH-1211 Geneva 4, Switzerland
[b] Department of Pharmacology–Toxicology, Trophos SA, Case 931, Parc Luminy Biotech Entreprises, F-13288 Marseille Cedex 09, France

Received 4 February 2005; accepted 13 June 2005

Abstract

Ligand-gated ion channels (LGICs) are cell surface proteins that play an important role in fast synaptic transmission and in the modulation of cellular activity. Due to their intrinsic properties, LGICs respond to neurotransmitters and other effectors (e.g. pH) and transduce the binding of a ligand into an electrical current on a microsecond timescale. Following activation, LGICs open allowing an ion flux across the cell membrane. Depending upon the charge and concentration of ions, the flux can cause a depolarization or hyperpolarization, thus modulating excitability of the cell. While our understanding of LGICs has significantly progressed during the past decade, many properties of these proteins are still poorly understood, in particular their modulation by allosteric effectors. LGICs are often thought as a simple on–off switches. However, a closer look at these receptors reveals a complex behavior and a wide repertoire of subtle modulation by intrinsic and extrinsic factors. From a physiological point of view, this modulation can be seen as an additional level of complexity in the cell signaling process.

Here we review the allosteric modulation of LGICs in light of the latest findings and discuss the suitability of this approach to the design of new therapeutic molecules.

Keywords: Ligand-gated ion channels; Allosteric modulation; P2X receptors; Glutamate receptors; Nicotinic acetylcholine receptors; nAChRs; Divalent cations

1. Ligand-gated ion channels

The capacity of the central nervous system (CNS) to process information depends upon the ability of neurons to communicate and thus on the intimate process of synaptic transmission. While numerous processes participate in synaptic transmission, the contribution of ligand-gated ion channels (LGICs) is certainly one of the determining steps. Although these integral membrane proteins have been the focus of attention of numerous studies, important facets regarding their function remain obscure.

In mammals, LGICs are divided into three main families according to the number of transmembrane segments present in the subunits that form the channels (Fig. 1A). As their name suggests, LGICs are proteins that span the cell membrane and form both the binding site for the natural ligand and the ion-conducting pore, which can be opened and closed by the binding of the ligand. These ion channels result from the assembly of subunits that form a water-filled, ion-selective pore. The subunit composition of these channels can be homomeric or heteromeric in nature and, as a result they display a great diversity of physiological and pharmacological properties.

The first LGIC family is the P2X (adenosine triphosphate, ATP) receptors; these are cationic channels and are thought to contain three subunits. Each subunit contains two transmembrane segments separated by a large extracellular loop [1–3], the N- and C-terminal regions are thought to be located intracellularly (Fig. 1A). To date, seven P2X subunits have been identified, each of which can form functional homomeric receptors, although some doubt exists on the ability of $P2X_6$ receptors to form functional homomers, see [4]. Functional heteromeric receptors containing the $P2X_{2/3}$, $P2X_{1/5}$, $P2X_{2/6}$ and $P2X_{4/6}$ subunits have been characterized in heterologous expression systems, several of these heteromeric receptors have biophysical and pharmacological properties similar to

* Corresponding author. Tel.: +41 22 379 53 55; fax: +41 22 379 54 02.
E-mail address: Ronald.Hogg@medecine.unige.ch (R.C. Hogg).
[1] These are the personal opinions of the author and do not necessarily represent those of Trophos.

0006-2952/$ – see front matter © 2005 Published by Elsevier Inc.
doi:10.1016/j.bcp.2005.06.010

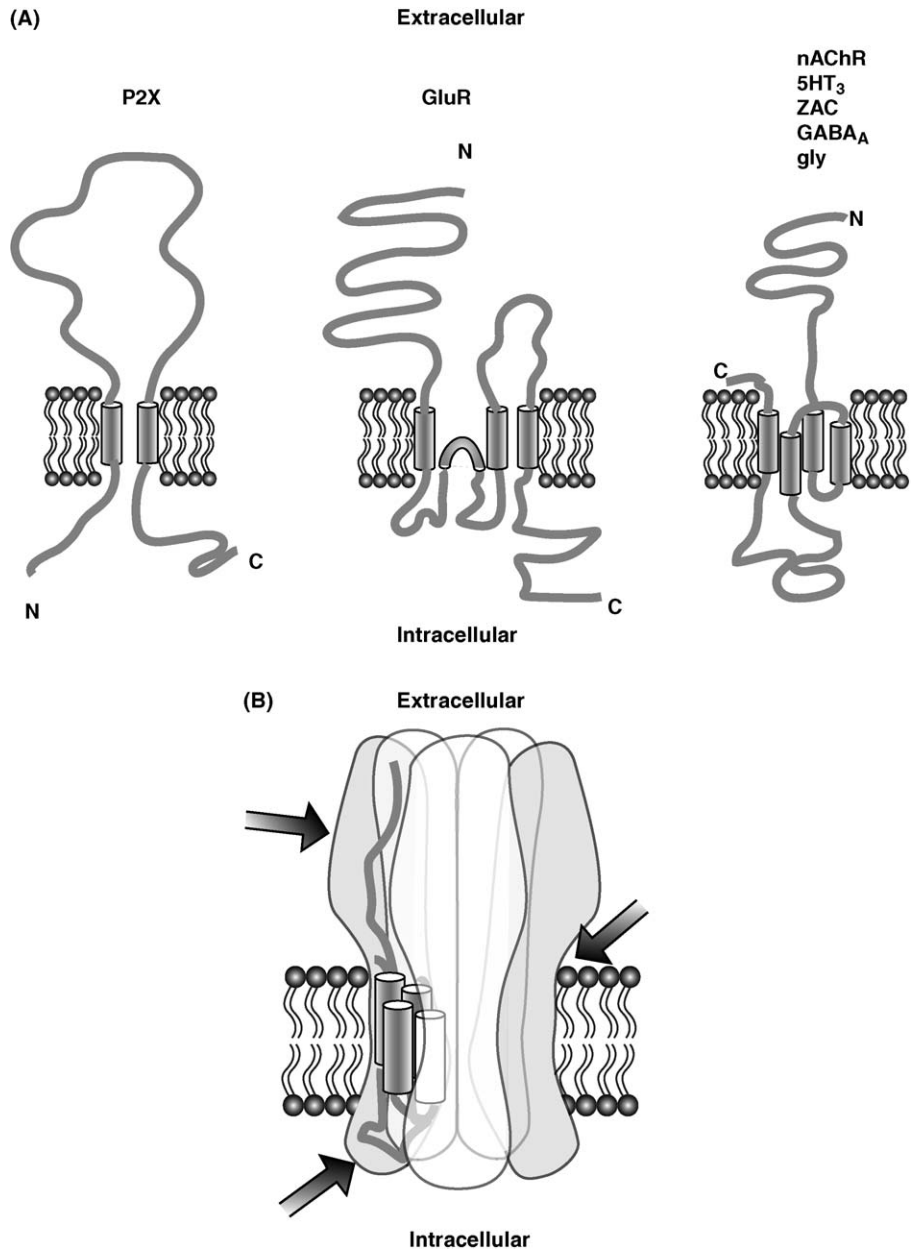

Fig. 1. Structure of the different LGICs. (A) Schematic representation of a single subunit from the three families of ligand-gated ion channels inserted in the cell membrane. Note the importance of both the extracellular and intracellular domain where different molecules can bind and interact. (B) Schematic representation of the typical structure of a four transmembrane LGIC such as the nAChR. Putative-binding sites for allosteric ligands are illustrated by the arrows.

native receptors suggesting that heteromeric P2X receptors may exist in native tissue. Immunoprecipitation experiments have shown that several other subunit combinations are also possible, and a number of alternatively spliced subunits have also been described [1–4].

The second family is the glutamate-activated cationic receptors, which include *N*-methyl-D-aspartate (NMDA) α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid (AMPA) and kainate receptors. These are made up of four homologous subunits. Each subunit contains an extracellular amino-terminal domain which makes up half of the agonist-binding region, the first two transmembrane segments are separated by a ''P-loop'' and the second half of the agonist-binding region is formed by the extracellular loop between the second and third transmembrane segments (Fig. 1A). The C-terminal tail is variable in length and protrudes into the cytoplasm [5]. In addition, many subunits undergo alternative splicing or RNA editing which further increases their functional diversity. Functional NMDA receptors are formed by the co-assembly of an NR1 subunit and one of the four types of NR2 (A–D) subunits [6]. AMPA receptors are composed of the GluR 1–4 subunits and kainate receptors from multimeric assemblies of GluR 5–7 and KA-1/2 subunits [7].

Finally, the third and largest family is the ''Cys-loop receptor superfamily'' so called because of a conserved