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Review

Calcium permeability of ligand-gated Ca^{2+} channels

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ABSTRACT

Many of cation-permeable ionotropic receptors to various neurotransmitters, such as glutamate, acetylcholine and ATP, are permeable to Ca^{2+} ions. For some of them, in particular NMDA, nicotinic Ach and P2X receptors, permeability to Ca^{2+} is higher than permeability to monovalent cations. Such receptors can be viewed as ligand-gated Ca^{2+}-channels (LGCCs). This review provides an overview of past works on structure LGCCs, including structural motifs responsible for their interaction with Ca^{2+} ions, and functional implications of their Ca^{2+}-permeability. The NMDA, P2X and nicotinic Ach receptors are abundantly expressed in the central nervous system. They are present at the nerve terminals, postsynaptic, extrasynaptic and glial membrane and therefore can contribute to synaptic function at different levels. Their heteromeric structure leads to wide variety of LGCC subtypes and great diversity of their functional properties. The influx of Ca^{2+} provided by LGCCs can activate a plethora of secondary messenger cascades, which can modulate activity, trafficking and lateral mobility of LGCCs and thereby are entangled with their physiological function. In the discussion of the physiological importance of LGCCs we are focusing on emerging evidence on their role in control of synaptic transmission, plasticity and glia–neuron interaction.

Contents

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1. The superfamily of ligand-gated cationic channels

The superfamily of ligand-gated Ca^{2+}-channels (LGCCs), also known as ionotropic receptors, is represented by three topologically different classes. These are the trimeric P2X purinoceptors, tetrameric glutamate receptors and pentameric receptors, that, in vertebrates, form receptors for acetylcholine and serotonin. In general, the LGCCs show relatively good selectivity only with respect to cation/anion division and relatively weak selectivity among different cations. Some of ionotropic receptors are more selective to divalent cations, in particular calcium. Importantly, there are specific types of LGCC responding to all three major excitatory neurotransmitters of the nervous system: glutamate (NMDA and some AMPA/KA receptors), acetylcholine (nicotinic nACh receptors) and ATP (P2X receptors) (Table 1). Due to their general cationic conductance, LGCCs can mediate an excitatory synaptic input and in some cases (P2X receptors and nACh receptors of peripheral neurons) can make main contribution to initiation of the action potential. Physiological significance of these channels, is also defined, by their ability to mediate Ca^{2+}-fluxes following activation by the neurotransmitter.

The three main types of LGCCs, namely NMDA, P2X and nACh receptors, have similar range of Ca^{2+}-permeability (Table 1) which confers to them similar physiological roles, as we shall outline in this review. Our review will be focused on these three LGCC types.

2. Molecular variety and tissue distribution of LGCCs

NMDA receptors are heteromeric complexes exhibiting variety of subtypes (Pachernegg et al., 2012; Paoletti et al., 2013; Traynelis et al., 2010). Expression of functional NMDA receptors requires two GluN1 subunits combined with one or two GluN2 (A,B,C,D) and/or GluN3(A,B) subunits (Matsuda et al., 2003; Furukawa et al., 2005; Traynelis et al., 2010). Number of possible compositions of NMDA receptor can be increased further by alternative splicing of genes encoding GluN1 and GluN3 subunits (Paoletti and Neyton, 2007; Traynelis et al., 2010). Subunit composition affects pharmacological and functional properties of NMDA receptors, including ion permeability and voltage-dependent channel block by extracellular Mg^{2+} (Paoletti et al., 2013; Traynelis et al., 2010).

Functional NMDA receptors are present at postsynaptic densities of many central synapses, although the expression of individual subunits exhibits regional specificity and undergoes significant developmental regulation (Paoletti et al., 2013). An example of such developmental regulation is a switch of NMDA RECEPTOR composition in neocortical, hippocampal and cerebellar synapses from GluN1/GluN2B in the first postnatal weeks to GluN1/GluN2A in young adult and mature ages (Traynelis et al., 2010). In the adult central synapses, there is a tendency (although it is not absolute) of segregated localisation of GluN2B subunits to extrasynaptic areas and GluN2A to postsynaptic densities (Traynelis et al., 2010; Paoletti

Table 1
Relative Ca^{2+}-permeability and fractional Ca^{2+} current of the NMDA, P2X, and nACh receptors in comparison with AMPA and Kainate receptors.

Receptor/experimental preparation	Relative Ca^{2+}-permeability		Fractional Ca^{2+} current	
	P_{Ca}/P_{mono}	Reference	Pf (%)	Reference
ATP (P2X) receptors				
Recombinant P2X1 receptors	3.9[c]	(Evans et al., 1996)	12.4	(Egan and Khakh, 2004)
Recombinant P2X2 receptors	2.2[c]	(Evans et al., 1996)	5.7	(Egan and Khakh, 2004)
Recombinant P2X3 receptors	1.2[c]	(Virginio et al., 1998)	2.7	(Egan and Khakh, 2004)
Recombinant P2X4 receptors	4.2	(Soto et al., 1996)	11.0	(Egan and Khakh, 2004)
P2X2/3 receptors from nodose neurones	1.5[c]	(Virginio et al., 1998)		
P2X2/3 receptors from DRG neurones	4.0[a,b,c]	(Lewis et al., 1995)		
P2X1 receptors of vas deferens	4.8[a,b,c]	(Valera et al., 1994)		
P2X receptors of pyramidal neocortical neurones	12.3	(Pankratov et al., 2002a)		
P2X1/5 receptors of neocortical astrocytes	2.2	(Palygin et al., 2010)		
NMDA receptors				
Recombinant GluN1/GluN2A	10.4	(Soto et al., 1996)	14.1	(Egan and Khakh, 2004)
Receptors	4.1[a,b]	(Burnashev et al., 1995)	11	(Burnashev et al., 1995)
Recombinant GluN1/GluN2C receptors	2.7[a,b]		8	(Burnashev et al., 1995)
Recombinant GluN1/GluN3A receptors	0.8	(Sasaki et al., 2002)		
NMDA RECEPTORs of CA1 pyramidal neurons	4.2	(Spruston et al., 1995)	10.7	(Garaschuk et al., 1996)
NMDA RECEPTORs of neocortical pyramidal neurons	7.5	(Palygin et al., 2011)		
tRIHETEROMERIC GluN1/GluN2/GluN3A receptors of cortical neurons	2.2–3.2	(Matsuda et al., 2003; Tong et al., 2008)		
NMDA RECEPTORs of neocortical astrocytes	3.1–3.4	(Palygin et al. 2010; Palygin et al. 2011)		
Ca^{2+}-permeable AMPA-receptors				
Recombinant unedited GluA1(Q) receptor	1.6[a,b]	(Burnashev et al., 1995)	3.2	(Burnashev et al., 1995)
Heteromeric GluA1(Q)/GluA2(R) receptor	0.54[a,b]	(Burnashev et al., 1995)	0.14	(Burnashev et al., 1995)
AMPA receptors of neocortical neurones	0.1–1.3	(Itazawa et al., 1997)		
AMPA receptors of CA1 pyramidal neurons			0.6	(Garaschuk et al., 1996)
Kainate receptors				
Recombinant KA receptors	0.39	(Burnashev et al., 1995)	0.8	(Burnashev et al., 1995)
GluR6 kainate receptors	0.4–1.2[d]	(Egebjerg and Heinemann, 1993)		
Neuronal ACh receptors				
Recombinant α7 receptors	4.0–6.6[c]	(Fucile et al., 2000)	8–11	(Fucile et al., 2003)
Hippocampal α7 receptors	6.1	(Castro and Albuquerque, 1995)		
Recombinant α4β2 receptors			3.1	(Egan and Khakh, 2004)

Methodology notes: if not pointed otherwise, the extended GHK constant field theory was used and corrections for activity were made; calcium permeability was evaluated in respect to Cs^+ (P_{Ca}/P_{Cs}).

[a] Not corrected for activity.
[b] Simplified GHK constant field theory was used.
[c] P_{Ca}/P_{Na}.
[d] P_{Ca}/P_{mono}.