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Modulatory action of metabotropic glutamate receptor (mGluR) 5 on mGluR1 function in striatal cholinergic interneurons

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Abstract

Within basal ganglia, group I metabotropic glutamate receptor subtypes (mGluR1 and 5) frequently co-localize in the same neuron. However, little is known about how these receptors functionally interact. We addressed this issue by means of electrophysiological recordings of striatal cholinergic interneurons, a neuronal subtype that co-express both group I mGluRs. The group I non-selective agonist 3,5-DHPG induced a membrane depolarization/inward current that was prevented by co-application of LY 367385, a selective mGluR1 antagonist, and SIB 1757 or MPEP, blockers of mGluR5 subtype. The reversal potential for the response to 3,5-DHPG was close to the equilibrium potential for potassium channels.

Repeated bath or focal applications of 3,5-DHPG induced a progressive decline in the amplitude of the membrane depolarization, suggesting that group I mGluRs undergo receptor desensitization. Interestingly, in the presence of the mGluR5 blocker, SIB 1757, this event was not observed, whereas it occurred in LY 367385. PKC blockers chelerythrine and calphostin C mimicked the inhibitory effect of SIB 1757. In a subset of interneurons, in MPEP or SIB 1757, 3,5-DHPG induced a 0.5–1 Hz oscillatory response, that was prevented by L-type Ca^{2+} channel blockers, and by the tyrosine kinase inhibitors genistein and lavendustin. Together, these data suggest that mGluR5 modulates mGluR1 activity to shape cell excitability.
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1. Introduction

Metabotropic glutamate receptors (mGluRs) are members of the group C, G protein-coupled receptor (GPCR) family of seven-transmembrane domain receptors. By alternative splicing eight genes generate more than 15 proteins, cloned and classified into three subgroups on the basis of their sequence similarity, pharmacology, and signal transduction mechanisms. mGluR1 and 5, group I members, are coupled to $G_{q/11}$ proteins and promote phosphoinositide hydrolysis via phospholipase C activation, whereas both group II (mGluR2 and 3) and group III (mGluR4, 6, 7, 8), though with some exceptions, are negatively coupled to adenylyl cyclase via G_i/G_o proteins and inhibit cAMP

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formation (for reviews, see De Blasi et al., 2001; Hermans and Challiss, 2001; Pin et al., 2003; Conn, 2003; Fagni et al., 2004).

MGluRs show a heterogeneous distribution pattern in the basal ganglia and have been implicated in a variety of physiological and pathophysiological actions (for reviews, see Rouse et al., 2000; Marino et al., 2002; Pisani et al., 2003; Gubellini et al., 2004). Interestingly, in different basal ganglia regions, group I mGluR1 and 5 are co-expressed in the same neuronal subtype and their high degree of sequence homology, together with their coupling to identical effectors in recombinant systems, have led to the assumption that these receptors would exhibit redundant functions. However, recent studies suggest that mGluR1 and 5 might accomplish distinct functional roles in the same neuron (Awad et al., 2000; Valenti et al., 2002; Poisik et al., 2003). In the striatum, distinct functional roles for group I mGluR subtypes have been demonstrated for medium spiny neurons, either in synaptic plasticity or in the modulation of NMDA receptor activity (Pisani et al., 2001a; Gubellini et al., 2004). Conversely, the activation of both mGluR1 and 5 has been shown to exert an excitatory action on striatal cholinergic interneurons (Takeshita et al., 1996; Pisani et al., 2001b; Bell et al., 2002). Thus, the functional significance of the cellular co-localization of group I mGluR subtypes still remains largely elusive. Cholinergic interneurons provide the striatum with a very high content of acetylcholine (ACh) (Bolam et al., 1984; Sidibè and Smith, 1999), therefore, playing a central role in the basal ganglia circuitry in the control of voluntary movements and in the pathophysiology of movement disorders (Calabresi et al., 2000; Pisani et al., 2003). Indeed, the control of striatal ACh content with anticholinergic drugs has long been the target in the therapy of movement disorders such as Parkinson's disease (PD) and dystonia (Duvoisin, 1967; Burke, 1986).

In the present work, an electrophysiological approach was utilized in order to assess the distinct roles exerted by mGluR1 and 5 in striatal cholinergic interneurons, and to explore the cellular mechanisms underlying their reciprocal interactions.

2. Materials and methods

2.1. Tissue preparation

The animal experiments were carried out in accordance with the guidelines of the European Communities Council Directive (86/609/EEC). All efforts were made to reduce the number of animals used and minimize their suffering. Preparation of corticostriatal slices was carried out as previously described (Pisani et al., 2001a,b, 2002). Male Wistar rats (3–4 weeks old) were killed by cervical dislocation under deep anaesthesia. The brain was rapidly removed from the skull and corticostriatal coronal slices (180–200 μm) were cut with a vibratome in oxygenated Krebs' solution (in mM: 126 NaCl, 2.5 KCl, 1.3 $MgCl_2$, 1.2 NaH_2PO_4, 2.4 $CaCl_2$, 10 glucose, 18 $NaHCO_3$). After 30 min recovery, a slice was transferred in the recording chamber (0.5–1 ml volume), on the stage of an upright microscope (BX51WI, Olympus, Milan, Italy), and submerged by oxygenated (95% O_2/5% CO_2) Krebs' solution flowing at 2.5–3 ml/min, 32–33 °C. The microscope was equipped with a 20×, 0.95 n.a. water immersion objective (XLUMPlan Fl, Olympus).

2.2. Optical set up and electrophysiology

A monochrome CCD camera (C6790, Hamamatsu, Japan) was used to visualize cholinergic interneurons on a PC monitor. Differential interference contrast optics (DIC, Nomarski) combined to infrared (IR) light were used to identify and impale under visual guidance cholinergic interneurons up to ~150 μm beneath the slice surface. Intracellular recordings were performed in the current-clamp mode using sharp micro-electrodes filled with 2 M KCl. An Axoclamp 2B amplifier (Axon Instruments, Foster City, CA, USA) and pClamp9 software were used for signal acquisition and off-line analysis.

For whole-cell patch-clamp recordings, borosilicate glass pipettes were filled with: (in mM) K^+-gluconate (125), NaCl (10), $CaCl_2$ (1.0), $MgCl_2$ (2.0), 1,2-bis-(2-aminophenoxy)-ethane-*N*,*N*,*N*,*N*-tetraacetic acid (BAPTA; 0.5), *N*-(2-hydroxyethyl)-piperazine-*N*-*s*-ethanesulfonic acid (HEPES; 19), guanosine triphosphate (GTP; 0.3), Mg-adenosine triphosphate (Mg-ATP; 1.0), adjusted to pH 7.3 with KOH. Electrophysiological signals were detected using an Axopatch 1D amplifier (Axon Instruments). Access resistances, measured in the voltage-clamp mode, were in the range of 5–30 MΩ prior to electronic compensation (60–80% was commonly used). Under voltage-clamp conditions, cells were clamped at −60 mV and series resistance (8–15 MΩ) was monitored during the course of the experiment by the peak amplitude of the capacitive transient induced by a −5-mV pulse. Neurons in which series resistance changed by more than 10% during drug application were discarded from the statistics. The current–voltage relationship was examined by applying voltage ramps (from −120 mV to −40 mV, 6 mV/s).

For focal application experiments, a patch pipette filled with 100 μM 3,5-DHPG was positioned close to the cell body of the recorded neuron and connected to a PV830 pneumatic picopump pressure ejection system (WPI Inc., Sarasota, FL, USA) set to 20 psi, 500 ms. Values given in the text and in the figures are

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