Neuroscience 274 (2014) 429–445

NEUROSCIENCE FOREFRONT REVIEW

METABOTROPIC GLUTAMATE RECEPTORS IN AUDITORY PROCESSING

Y. LU *

Department of Anatomy and Neurobiology, College of Medicine, Northeast Ohio Medical University, Rootstown, OH 44272, USA

Abstract—As the major excitatory neurotransmitter used in the vertebrate brain, glutamate activates ionotropic and metabotropic glutamate receptors (mGluRs), which mediate fast and slow neuronal actions, respectively. Important modulatory roles of mGluRs have been shown in many brain areas, and drugs targeting mGluRs have been developed for the treatment of brain disorders. Here, I review studies on mGluRs in the auditory system. Anatomical expression of mGluRs in the cochlear nucleus has been well characterized, while data for other auditory nuclei await more systematic investigations at both the light and electron microscopy levels. The physiology of mGluRs has been extensively studied using *in vitro* brain slice preparations, with a focus on the lower auditory brainstem in both mammals and birds. These *in vitro* physiological studies have revealed that mGluRs participate in neurotransmission, regulate ionic homeostasis, induce synaptic plasticity, and maintain the balance between excitation and inhibition in a variety of auditory structures. However, very few *in vivo* physiological studies on mGluRs in auditory processing have been undertaken at the systems level. Many questions regarding the essential roles of mGluRs in auditory processing still remain unanswered and more rigorous basic research is warranted.

Key words: mGluR, auditory processing, neurotransmission, neuromodulation, excitotoxicity, synaptic plasticity.

Contents

*Tel: +1-330-325-6656; fax: +1-330-325-5916.
E-mail address: ylu@neomed.edu

Abbreviations: AC, auditory cortex; AVCN, anteroventral cochlear nucleus; CN, cochlear nucleus; DCN, dorsal cochlear nucleus; EPSC/P, excitatory postsynaptic current/potential; $GABA_BR$, $GABA_B$ receptor; GIRK, G-protein-coupled inward rectifier K^+; HF, high-frequency; IC, inferior colliculus; IHC, inner hair cell; IPSC/P, inhibitory postsynaptic current/potential; LF, low frequency; LSO, lateral superior olive; LTD/P, long-term depression/potentiation; MF, middle-frequency; MGB, medial geniculate body; mGluR, metabotropic glutamate receptor; MNTB, medial nucleus of trapzoid body; MSO, medial superior olive; NA, nucleus angularis; NL, nucleus laminaris; NM, nucleus magnocellularis; OHC, outer hair cell; PVCN, posteroventral cochlear nucleus; SON, superior olivary nucleus; VCN, ventral cochlear nucleus; VGCC, voltage-gated Ca^{2+} channel.

http://dx.doi.org/10.1016/j.neuroscience.2014.05.057
0306-4522/

INTRODUCTION

Glutamate is the most abundant excitatory neurotransmitter in the vertebrate brain. Upon release at synapses glutamate activates ionotropic receptor channels and metabotropic glutamate receptors (mGluRs), which mediate fast and slow neuronal actions, respectively. Since the discovery of mGluRs nearly 30 years ago (Sladeczek et al., 1985; Nicoletti et al., 1986a,b), eight members of mGluRs have been identified. They have been divided into three groups (group I: mGluR1 and 5; group II: mGluR2 and 3; and group III: mGluR4, 6, 7, and 8) based on their amino acid sequence, pharmacological properties, and signaling transduction pathways (reviewed in Niswender and Conn, 2010). mGluRs are expressed throughout the peripheral and central nervous system, exhibit a high degree of homology across different animal species, and exert neuromodulatory actions via multiple signaling pathways (reviewed in Ferraguti and Shigemoto, 2006; Nicoletti et al., 2011; Tharmalingam et al., 2012). Group I mGluRs are predominantly expressed at postsynaptic loci and are coupled primarily to G_q/G_{11} proteins associated with stimulation of the phospholipase C pathway. Group II and III mGluRs are predominantly expressed at presynaptic loci and are coupled to G_i/G_o proteins associated with inhibition of the adenylyl cyclase pathway. Because of their important modulatory roles under physiological as well as pathological conditions, mGluRs have been implicated in multiple brain disorders (reviewed in Swanson et al., 2005; Krystal et al., 2010), and drugs targeting mGluRs have been on clinical trials for the treatment of schizophrenia (Patil et al., 2007) and autism (Oberman, 2012). While this review is focused on mGluRs in the auditory system, readers are referred to several excellent reviews on the general topics of mGluRs (Cartmell and Schoepp, 2000; Pinheiro and Mulle, 2008; Olive, 2009; Krystal et al., 2010; Niswender and Conn, 2010; Nicoletti et al., 2011; Lodge et al., 2013).

At all levels of the auditory system, it is conceivable that mGluRs are involved in information processing, considering that glutamate is used as the major excitatory neurotransmitter from the peripheral hearing organ (the cochlea) all the way up to the auditory cortex (AC), and that mGluRs have been found to be expressed in a variety of auditory structures. Understanding the anatomy and physiology of mGluRs at various levels of the auditory system will not only provide an in-depth understanding of mechanisms that underlie auditory processing, but may also help design potential therapeutic approaches targeting mGluRs for the treatment of hearing disorders. Here, I will first review the anatomical expression and physiology of mGluRs in the mammalian auditory system, with a focus on the cochlea, a number of nuclei in the lower auditory brainstem, the auditory midbrain, the auditory thalamus, and the AC. Then, I will review studies of mGluRs in the avian lower auditory brainstem, and propose directions for future studies.

OVERVIEW OF ANATOMICAL EXPRESSION OF MGLURS IN THE MAMMALIAN AUDITORY SYSTEM AND CONSIDERATION OF PHYSIOLOGICAL METHODS

Anatomical data on the expression of mGluRs in the mammalian auditory system are summarized in Table 1. Data are extracted primarily from two sources. First, data are available from anatomical studies where the expression of mGluRs is examined throughout the whole brain (e.g., Shigemoto et al., 1992; Ohishi et al., 1993a,b, 1995, 1998; Bradley et al., 1998). Because the auditory system is not the focus of these studies, the data on mGluR expression in the auditory system lack details. An exception to this lack of details may be the data on the expression of mGluRs in the cochlear nucleus (CN), which has been studied more in-depth than any other auditory structure (Ohishi et al., 1995, 1998; Wright et al., 1996; Petralia et al., 1996a, 1997; Bilak and Morest, 1998; Bradley et al., 1998; Kinoshita et al., 1998; Kemmer and Vater, 2001; Irie et al., 2006; Dino and Mugnaini, 2008). Second, data on the expression of mGluRs in the auditory system are available from physiological studies where anatomical data were obtained to support the physiology (e.g., Kushmerick et al., 2004; Nishimaki et al., 2007; Lee and Sherman, 2012), but generally, these studies did not provide in-depth details about the anatomy of mGluRs. Overall, the anatomical data of mGluRs in the auditory system are far from being complete. However, one general impression is that mGluRs are extensively expressed in cells at various levels of the auditory system. In order to understand the roles of mGluRs in auditory processing one key future direction is to systematically investigate the expression of mGluRs in the auditory system, both at the light and electron microscopy levels.

Most physiological studies on mGluRs in the central auditory system have been performed using *in vitro* brain slice preparations. The use of *in vitro* brain slices allows for stable and reliable intracellular whole-cell recordings for long periods of time (Dingledine et al., 1980; Trussell, 1999), making possible studies of both short- and long-term effects of mGluRs on neuronal properties. This approach also allows for application of pharmacological agents at known concentrations. Precise control of the concentration of pharmacological agents is especially critical for studying the effects of mGluR agonists and antagonists, considering that subtype or group member specificity of drugs can be concentration specific (reviewed by Nicoletti et al., 2011). The physiological results reviewed below are obtained using whole-cell recordings in brain slices, unless indicated otherwise. It is worthwhile to mention an advanced patch recording method, perforated patch recording. Because perforated patch recording can better preserve the intracellular signaling molecules (Horn and Marty, 1988; Kyrozis and Reichling, 1995; Fan and Palade, 1998), it is particularly useful when examining the effect of mGluRs in postsynaptic cells. It is known that under whole-cell recording mode, one could potentially wash out