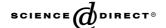
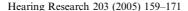


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Synaptic transmission mediated by ionotropic glutamate, glycine and GABA receptors in the rat's ventral nucleus of the lateral lemniscus

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Abstract

The synaptic pharmacology of the ventral nucleus of the lateral lemniscus (VNLL) was investigated in brain slices obtained from rats of 14–37 days old using intracellular recording techniques. Excitatory and inhibitory synaptic potentials (EPSPs and IPSPs) were elicited by electrical stimulation of the lemniscal pathway and recorded from neurons with five types of intrinsic firing patterns (onset, pause, adapting, regular and bursting types). Synaptic receptors that mediated the EPSPs and IPSPs were identified using AMPA, NMDA, GABA_A and glycine receptor antagonists. The early/short EPSPs were mediated by AMPA receptors. The late/long EPSPs, encountered only in neurons of younger animals, were mediated by NMDA receptors. The IPSPs in most neurons were mediated by glycine receptors. In some neurons the IPSPs were mediated by GABA_A receptors or both glycine and GABA_A receptors. The temporal dynamics of fast AMPA EPSPs and glycinergic IPSPs were very similar. AMPA EPSPs and glycinergic (and/or GABAergic) IPSPs could be encountered in a single neuron. The results suggest that the VNLL not only relays incoming signals rapidly from the lower brainstem to the inferior colliculus, but also integrates excitatory and inhibitory inputs to modify and process auditory information.

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Keywords: Auditory system; Intracellular recording; AMPA receptor; Postsynaptic potential; Brain slice

1. Introduction

The ventral nucleus of the lateral lemniscus (VNLL) lies among the fibers of the lateral lemniscus that links

Abbreviations: ACSF, artificial cerebrospinal fluid; AMPA, alpha-amino-3-hydroxy-5-methylisoxazole-4 propionic acid; APV, L-2-amino-5-phosphonovaleric acid; CN, cochlear nucleus; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; HEPES, *N*-[2-Hydroxy-ethyl]piperazine-*N*'-[2-ethanesulfonic acid]; IC, inferior colliculus; IPSP, inhibitory postsynaptic potential; LNTB, lateral nucleus of the trapezoid body; MNTB, medial nucleus of the trapezoid body; NMDA, *N*-methyl-D-aspartate; PSTH, post-stimulus time histogram; VCN, ventral cochlear nucleus; VNLL, ventral nucleus of the lateral lemniscus; VNTB, ventral nucleus of the trapezoid body

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the auditory lower brainstem and midbrain. The VNLL mainly receives inputs from the contralateral ventral cochlear nucleus (VCN) and is generally believed to be a monaural nucleus (Cant, 1992; Schwartz, 1992). All the major types of cells in the VCN project to the VNLL (Zook and Casseday, 1985; Friauf and Ostwald, 1988; Vater and Feng, 1990; Smith et al., 1991, 1993a,b; Huffman and Covey, 1995; Adams, 1997; Schofield and Cant, 1997; Vater et al., 1997). Since these VCN neurons are considered to be excitatory, the contralateral projections are excitatory in nature (Oertel and Wickesberg, 2002). The VNLL also receives minor projections from the ipsilateral VCN, periolivary nuclei, and lateral, ventral and medial nuclei of the trapezoid body (LNTB, VNTB and MNTB) (Glendenning et al., 1981; Spangler et al., 1985; Huffman and Covey, 1995; Warr and Beck, 1996; Schofield and Cant, 1997). Principal neurons in the MNTB are known to be immunoreactive for glycine, and neurons in the LNTB and VNTB for GABA and/or glycine (Helfert et al., 1989; Vater et al., 1992; Helfert and Aschoff, 1997). Therefore, while the three nuclei of the trapezoid body may all provide glycinergic projections to the VNLL, the LNTB and VNTB could also provide GABAergic projections.

The major target of the VNLL is the ipsilateral inferior colliculus (IC) (Brunso-Bechtold et al., 1981; Kudo, 1981; Whitley and Henkel, 1984; Covey and Casseday, 1986). A small number of VNLL neurons also project to the contralateral IC (Nordeen et al., 1983; Whitley and Henkel, 1984; Moore, 1988). Immunocytochemical studies have revealed that most VNLL neurons are GABAergic and/or glycinergic (González-Hernández et al., 1996; Saint Marie et al., 1997; Vater et al., 1997; Zhang et al., 1998; Riquelme et al., 2001). Among lower brainstem structures the VNLL is possibly the single largest source of inhibition providing projections to the IC (Saint Marie and Baker, 1990). Therefore, the VNLL may play a significant role in shaping and modulating auditory responses of IC neurons.

There are a few electrophysiological studies on response characteristics of VNLL neurons to acoustic stimulation (Aitkin et al., 1970; Guinan et al., 1972a,b; Covey and Casseday, 1991; Adams, 1997; Huffman et al., 1998a,b; Batra and Fitzpatrick, 1997, 1999, 2002). However, how VNLL neurons contribute to the processing of auditory information is not well understood.

Our previous studies with intracellular and whole-cell patch clamp recordings in brain slice preparations have investigated the intrinsic membrane properties of rat's VNLL neurons and classified neurons based on their responses to intracellular current injection, revealing onset, regular, pause, adapting and bursting cell types (Wu, 1999; Zhao and Wu, 2001). The results indicate that the VNLL is a heterogeneous neuronal group and it may process different aspects of auditory information.

Intracellular labeling has shown a variety of morphological cell types. There is a correlation between a cell's intrinsic physiological characteristics and its morphological features in the rat's VNLL (Zhao and Wu, 2001). Onset cells have a bushy-like dendritic profile. Regular and pause neurons have a stellate profile with relatively less branched dendrites compared to onset cells. Adapting neurons are also stellate in shape, but with a large and less-branched dendritic tree. Bursting neurons have a fusiform shaped cell body and a dendritic arbor that is parallel to the long axis of the cell body and orthogonal to the fibers of the lemniscal fibers. Different physiological and morphological types of neurons are observed throughout the VNLL, although onset, regular, and pause neurons are more prevalent in the ventral part, and adapting and bursting neurons are more prevalent in the dorsal part of the VNLL.

Previous studies have also investigated synaptic responses in VNLL neurons and found that excitatory and inhibitory synaptic potentials (EPSPs and IPSPs) could be elicited by stimulation of the lateral lemniscus (Wu, 1999; Zhao and Wu, 2001). Both EPSPs and IPSPs could be observed in a single VNLL neuron. The outcome of synaptic responses was determined by the interplay between excitatory and inhibitory postsynaptic potentials.

So far, the synaptic receptors that mediate excitatory and inhibitory synaptic transmission in the VNLL have not been identified. In this study, we applied specific receptor antagonists to dissect synaptic responses and to identify the receptor types that mediated postsynaptic potentials. We studied the incidence and kinetic properties of synaptic responses that were mediated by different excitatory and inhibitory neurotransmitter receptors. We also examined whether there was any relationship between the receptor type and the intrinsic firing pattern.

2. Methods

Brain slices were obtained from young albino rats (Wistar strain, Charles River Co., Que., Canada) during postnatal day 14–37 using the procedure described in our previous reports (Wu, 1999; Zhao and Wu, 2001). The procedure was approved by the Carleton University Animal Care Committee and was in accordance with the guidelines of the Canadian Council on Animal Care. Briefly, the rats were first anesthetized by halothane and then decapitated. The brain was extracted and submerged in a dish containing warm (~32 °C) oxygenated artificial cerebrospinal fluid (ACSF). The ACSF consisted of (in mM): 129 NaCl, 3 KCl, 1.2 KH₂PO₄, 2.4 CaCl₂, 1.3 MgSO₄, 20 NaHCO₃, 3 N-[2-hydroxyethyl|piperazine-N'-[2-ethanesulfonic acid] (HEPES) and 10 glucose in distilled water, and was saturated with 95% O_2 -5% CO_2 . The pH was maintained at about 7.4 after complete saturation with O₂–CO₂. Brain slices of 400 µm were made in the frontal plane through the VNLL using a tissue slicer (Campden Instruments, Sileby, Leics, UK). The slice was then placed in a small recording chamber and perfused with oxygenated ACSF at a rate of 8–10 ml/min. The temperature of the ACSF in the chamber was \sim 34 °C. The slice was perfused for about 1 h before any recordings were made. The brain slice was illuminated from below the recording chamber by light passing through a darkfield condenser, and the VNLL was visible with a Leitz dissecting microscope.

Intracellular recordings were made with glass micropipettes filled with 4 M potassium acetate. The electrode impedance was 130–180 M Ω . The recording site in the VNLL was randomly selected throughout the entire structure. The electrode was positioned onto the surface

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