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Long-term Potentiation in the Dorsal Nucleus of the Lateral Lemniscus and Central Nucleus of the Inferior Colliculus in the Rat

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Master of Science
Specialization in Neuroscience

Department of Psychology and Institute of Neuroscience
Carleton University
Ottawa, Ontario
July, 1999

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submitted by
Yan Zhang, B.Sc.

in partial fulfillment of the requirement for the degree
of Master of Science
Specialization in Neuroscience

Chair, Department of Psychology

Thesis Supervisor

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July, 1999

Abstract

The purpose of this study is to determine whether long-term potentiation (LTP) can be induced in the dorsal nucleus of the lateral lemniscus (DNLL) and central nucleus of the inferior colliculus (ICC) by electrical stimulation of the lateral lemniscus (LL). If LTP can be induced, is it mediated by *N*-methyl-D-aspartate (NMDA) and/or other receptors?

Brain slices of the DNLL and ICC were obtained from young (14-35 days old) Wistar rats. The evoked field potentials were recorded from the DNLL and ICC, respectively. After tetanic stimulation (50 Hz, 20 s) of the LL, LTP was observed in 30.9% cases of the DNLL and in 82.9% cases of the ICC. Induction of LTP in the ICC required activation of both NMDA and γ -aminobutyric acid_B (GABA_B) receptors. Intracellular recording from ICC neurons further demonstrated a possible cellular mechanism of GABA_B receptors in induction of LTP.

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List of Abbreviations

ACSF	artificial cerebrospinal fluid
APV	D,L-2-amino-5-phosphonovaleric acid
ATP	adenosine triphosphate
AVCN	anteroventral cochlear nucleus
Baclofen	(+,-)- β -(aminomethyl)-4-chlorobenzenepropanoic acid
Bicuculline	[R-(R*,S*)]-6-(5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-g]-isoquinidin-5-yl)-furo[3,4-e]-1,3-benzodioxo-8-(6H)-one
α -CamKII	α -calcium-calmodulin-dependent kinase II
cGMP	cyclic guanosin monophosphate
CGP35348	3-amino-propyl(diethoxymethyl)-phosphinic acid
CGP55845	3-N[1-(S)-(3,4-dichlorophenyl)ethyl]amino-2-(S)-hydroxypropyl- <i>P</i> -benzyl-phosphinic
CN	cochlear nucleus (complex)
CNQX	6-cyano-7-nitro-quinoxaline-2,3-dione
CNS	central nervous system
CP	commissure of Probst
DCN	dorsal cochlear nucleus
DGG	γ -D-glutamylglycine
DNLL	dorsal nucleus of lateral lemniscus
DNQX	6,7-dinitroquinoxaline-2,3(1H,4H)-dione
EPSP	excitatory postsynaptic potential
GABA	γ -aminobutyric acid
GAD	glutamic acid decarboxylase
HEPES	3 <i>N</i> -2-hydroxyethylpiperazine- <i>N'</i> -2-ethanesulfonic acid
HRP	horseradish peroxidase
5-HT ₃	5-hydroxytryptamine (3)

IC	inferior colliculus
ICC	central nucleus of inferior colliculus
ID	inner diameter
IPSC	inhibitory postsynaptic current
IPSP	inhibitory postsynaptic potential
LL	lateral lemniscus
LSO	lateral superior olive nucleus
LTD	long-term depression
LTP	long-term potentiation
mGluR	metabotropic glutamate receptor
MNTB	medial nucleus of trapezoid body
MSO	medial superior olive nucleus
Muscimol	5-aminomethyl-3-hydroxyisoxazole
nLL	nuclei of the lateral lemniscus
NMDA	γ -methyl-D-aspartic acid
NO	nitric oxide
NOS	nitric oxide synthase
OD	outer diameter
Phaclofen	3-amino-2-(4-chlorophenyl)propylphosphonic acid
PKC	protein kinase C
PVCN	posteroventral cochlear nucleus
Saclofen	β -(aminomethyl)-4-chloro-benzeneethanesulfonic acid
SC	superior colliculus
Sch	Schaffer collateral-commissural pathway
SOC	superior olivary complex
SPSS	Statistics Package of Social Sciences
VCN	ventral cochlear nucleus

VNLL ventral nucleus of lateral lemniscus

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Introduction

1. Auditory Brain Stem and Midbrain Pathway

The auditory pathway in mammals is very complicated. The major components of the mammalian auditory brain stem and midbrain pathway are the following: cochlear nucleus complex, superior olivary complex, nuclei of the lateral lemniscus and inferior colliculus.

The cochlear nuclear complex (CN) is a remarkable structure located on the posterolateral surface of the brain stem at the junction of the pons and the medulla (Musiek and Lamb, 1992). Auditory nerve fibers enter the different parts of CN according to their response to sound frequencies. The CN receives afferent inputs usually from the ipsilateral cochlea through the auditory nerves.

The superior olivary complex (SOC) is located ventrally and medially to the CN in the caudal pons. There are several individual nuclei within the SOC: the lateral superior olive (LSO), the medial superior olive (MSO), the nuclei of the trapezoid body, and the lateral and medial preolivary nuclei (Musiek and Lamb, 1992).

The lateral lemniscus (LL) is a major brainstem auditory pathway that includes both ascending and descending fibers (Musiek and Lamb, 1992). The nuclei of lateral lemniscus (nLL) are embedded in the LL fibers and usually grouped into two parts: the ventral (VNLL) and dorsal nuclei (DNLL). The nLL receive afferent inputs from the dorsal CN (DCN) on the contralateral side as well as the ventral CN (VCN) on

both sides of the brain. Both the ipsilateral and contralateral SOC nuclei provide inputs to the nLL. The DNLL on each side of the brain is interconnected by the commissure of Probst (CP). Most of the DNLL neurons can be activated binaurally in contrast with the majority of the VNLL neurons, which respond to only contralateral stimulation (Musiek and Lamb, 1992).

The inferior colliculus (IC) is located on the dorsal surface of the midbrain. A majority of auditory fibers from the LL and lower auditory structures synapse directly or indirectly at the IC. There are a large number of interneurons in the IC, suggesting strong neuronal interconnections and interactions (Morest and Oliver, 1984).

Figure 1 (from Wu, 1999) shows a photomicrograph of a cresyl violet-stained frontal section through the midbrain and LL to illustrate the positions of the ICC, DNLL, VNLL and CP on one brain slice.

---- Insert Figure 1 About Here ----

2. The Dorsal Nucleus of the Lateral Lemniscus

The DNLL is a prominent gathering place of neurons within the LL, bordered laterally by the nucleus sagulum and ventrally by the VNLL (Bajo et al., 1993; Glendenning et al., 1981; Hutson et al., 1991; Kane and Barone, 1980; Shneiderman et al., 1988).

2.1. Major Inputs and Outputs of the DNLL

The major sources of ascending inputs to the DNLL are the contralateral DCN (Adams, 1979; Adams and Warr, 1976; Fernandez and Karapas, 1967), contralateral anterior ventral division of the CN (AVCN), contralateral posterior ventral division of the CN (PVCN), ipsilateral MSO, and bilateral LSO (Elverland, 1978; Glendenning et al., 1981; Glendenning and Masterton, 1983; Henkel and Spangler, 1983; Huston et al., 1991; Kudo, 1981; Schwartz, 1991; Shneiderman et al., 1988). Substantially smaller input to the DNLL originates from the ipsilateral VNLL (Glendenning et al., 1981; Warr, 1966, 1982).

The DNLL also receives input from the contralateral DNLL via the CP (Goldberg and Moore, 1967; Oliver and Shneiderman, 1989; Papez, 1929). Most of the fibers within the CP probably have their origins in the contralateral DNLL (Goldberg and Moore, 1967; Huston et al., 1991; Kudo, 1981).

The descending sources to the DNLL include ipsilateral IC (Foster and Hall, 1978; Goldberg and Moore, 1967; Zook and Casseday, 1979) and, possibly, superior colliculus (SC) as well (Edwards et al., 1979; Grafova et al., 1978; Schwartz, 1991).

In the cat, projections from the low-frequency areas terminate in the dorsal part of the DNLL, while those from the high-frequency areas project to the ventral DNLL (Shneiderman et al., 1988). In the rat, the projection pattern of DNLL is described as concentric or “onion-like” with high frequencies represented by the outer layer of cells and lower frequencies by the inner layer of cells (Kelly, 1997; Merchán et al., 1994).

The DNLL sends projections to the ipsilateral ICC as well as to the contralateral DNLL and ICC through the CP (Bajo et al., 1993; González-Hernández et al., 1996; Ito et al., 1996; Kelly et al., 1998b; Labelle and Kelly, 1996; Merchán et al., 1994; Tanaka et al., 1985; van Adel et al., 1996, 1997; van Adel and Kelly, 1998). Cells projecting to the IC in the rat are found in the caudal part of the DNLL (Tanaka et al., 1985). Several researchers have suggested that the ipsilateral and contralateral projections from the DNLL to IC come from different populations of neurons in the DNLL. Cells projecting to the ipsilateral IC are found central and lateral in the DNLL, whereas those to the contralateral IC are medially located in the DNLL. A few neurons project to both ipsilateral and contralateral ICs (Ito et al., 1996; Merchán et al., 1994; Schwartz, 1991; Tanaka et al., 1985; van Adel et al., 1997). In the rat, cell counting data indicate that the contralaterally projecting DNLL neurons account for approximately 70-75% of the total number of cells projecting to IC via the CP (González-Hernández et al., 1996; Ito et al., 1996; Tanaka et al., 1985).

A different group of neurons in the rostral DNLL project to the SC (Tanaka et al., 1985). The DNLL also projects to the SOC (Elverland, 1977, 1978), VNLL (Adams, 1979), and CN (Kane and Conlee, 1979; Kane and Finn, 1977; Schwartz, 1991).

2.2. Attributes of the Projections to the DNLL

Excitatory projections to the DNLL probably come from the neurons in the contralateral CN, the contralateral LSO, and the ipsilateral MSO (Kelly, 1997; Wu, 1998).

In the cat, the central nucleus of inferior colliculus (ICC) receives a heavy glycinergic projection from the ipsilateral LSO (Saint-Marie and Baker, 1990; Saint-Marie et al., 1989), which probably sends parallel or collateralized projections to the DNLL as well (Glendenning and Masterton, 1983; Glendenning et al., 1985, 1992). Wu and Kelly (1993, 1996) reported that the glycine receptor antagonist, strychnine, effectively blocked ipsilateral inhibitory postsynaptic potentials (IPSPs) in brain slice preparations of the rat's DNLL. These results suggest that DNLL may receive a glycinergic projection from the ipsilateral LSO (Wu and Kelly, 1996). In addition, some cells in the VNLL of rat are immunoreactive for glycine (Aoki et al., 1988) and, therefore, the VNLL may be another source of inhibition in the lemniscal projection to the DNLL (Glendenning et al., 1981, 1992; Shneiderman et al., 1988; Yang and Pollak, 1994).

In the DNLL, the IPSPs evoked by electrical stimulation of the LL were blocked by the glycine receptor antagonist, strychnine, but not the γ -aminobutyric acid (GABA)_A receptor antagonist, bicuculline, whereas the IPSPs elicited by the stimulation at the CP were blocked by bicuculline but not strychnine (Wu and Kelly, 1996). These results suggest that the inhibition from the LL is mediated by glycinergic neurons; in contrast, the inhibition from the contralateral DNLL is GABAergic. There is general agreement that the DNLL is a prominent GABAergic nucleus in the

auditory system and that one of its major projections is to the contralateral DNLL through the CP (Kelly, 1997; Wu, 1998) (Figure 2).

---- Insert Figure 2 About Here ----

2.3. Electrical and Chemical Properties of the DNLL Neurons

In a study of biocytin-labeled neurons in the DNLL, Wu and Kelly (1995b) reported a diversity of morphological cell types: multipolar; elongate I, II and III; and round. Recordings of postsynaptic responses indicate that DNLL cells of all types receive substantial convergence of synaptic activity from commissural and lemniscal sources (Wu and Kelly, 1995b).

An *in vitro* study (Wu and Kelly, 1995a) shown that all the cells in the DNLL were found to have linear current-voltage curves similar to those found in stellate cells in the VCN (Oertel et al., 1988; Wu and Oertel, 1984), various cell types in the DCN (Oertel and Wu, 1989; Zhang and Oertel, 1993a, b), and neurons in the LSO (Sanes, 1990, 1993; Wu and Kelly, 1991). Action potentials in the DNLL neurons could be followed by either a single or double undershoot, with a slow recovery to baseline in both cases. The fast component of the double undershoot is probably related to a voltage-sensitive K^+ current and the slow one with a Ca^{2+} -activated K^+ current (Hirsch and Oertel, 1988; Oertel, 1991; Wu and Kelly, 1995a).

Immunolabelling studies have suggested that most of the DNLL neurons are GABAergic (Adams and Mugnaini, 1984; Glendenning and Baker, 1988; Moore and

Moore, 1987; Roberts and Ribak, 1987; Shneiderman and Oliver, 1989; Thompson et al., 1985; Vater et al., 1992; Winer et al., 1995). Destruction of the DNLL results in a decrease in the evoked release of GABA in the IC with the greatest reduction contralateral to the damaged DNLL (Shneiderman et al., 1993). In Zhang et al.'s study (1998), GABA immunoreactivity and retrograde labeling by a tracer injected into one side of the IC were found in the same neurons in the bilateral DNLL. This study not only supports the earlier immunohistochemical results that the most of DNLL neurons are GABAergic (Adams and Mugaini, 1984; Moore and Moore, 1987; Roberts and Ribak, 1987; Shneiderman et al., 1993), but also provides a direct evidence of GABAergic projection from the DNLL to IC.

In the brain slice preparation, both excitatory and inhibitory postsynaptic responses can be found in the DNLL by electrical stimulation of either the LL or CP. Two kinds of excitatory postsynaptic potentials (EPSPs) were found in the same postsynaptic neurons in the DNLL: short-latency and longer-latency EPSPs. The short-latency EPSPs were blocked by the non-*N*-methyl-D-aspartate (non-NMDA) receptor antagonist, 6-cyano-7-nitro-quinoxaline-2,3-dione (CNQX), and the longer-latency EPSPs were blocked by D,L-2-amino-5-phosphonovaleric acid (APV), the NMDA receptor antagonist, but never by CNQX (Fu et al., 1997; Wu and Kelly, 1996). These results indicate that both non-NMDA and NMDA receptors exist in the DNLL neurons, probably on the same cell.

As mentioned above, the IPSPs in the DNLL evoked by electrically stimulating the LL could be blocked by strychnine (Wu and Kelly, 1996). This

suggests the existence of glycine receptors on the DNLL neurons. The IPSPs elicited by stimulation at the CP could be blocked by bath application of the GABA_A receptor antagonist, bicuculline, which indicates the presence of GABA_A receptors on the DNLL neurons as well (Wu and Kelly, 1996).

2.4. Physiology of the DNLL

In general, most neurons in the DNLL of rat are excited by contralateral acoustic stimulation and inhibited by ipsilateral stimulation (Kelly et al., 1998a). Similar binaural response patterns have been reported in the DNLL of the cat, big brown bat and mustache bat (Brugge et al., 1970; Covey, 1993; Covey and Casseday, 1995; Markovitz and Pollak, 1994).

In the cat, it was reported that 88% of units in the DNLL were binaural while the remaining units were monaural (Aitkin et al., 1970). In the big brown bat (*Eptesicus fuscus*), Covey (1993) found that in the caudal part of DNLL, 84% of the sampled neurons were binaural, while in the rostral part, 29% neurons were binaural. The active participation of the DNLL in binaural processing has been demonstrated by recording physiological responses from auditory cortex in the rats with unilateral kainic acid, an excitatory amino acid, lesions of DNLL (Glenn and Kelly, 1992). Animals with DNLL lesions shown reduced binaural suppression of evoked responses in the hemisphere contralateral to the lesion. Furthermore, a reversible blockade of DNLL activity by local injection of kynurenic acid altered the binaural response

properties of single neurons in the contralateral ICC, i.e., the inhibition associated with stimulation of the ipsilateral ear was reduced (Li and Kelly, 1992).

3. The Inferior Colliculus

3.1. Major Divisions of the IC

It is generally accepted that the IC in the rat can be divided into three main divisions: the central nucleus, the external cortex and the dorsal cortex. The central nucleus is characterized by a lamellar organization of disc-shaped neurons interspersed with multipolar cells. Both the external and dorsal cortices have three layers. The external cortex is located laterally, rostrally and ventrally to the central nucleus, and the dorsal cortex is located dorsocaudally and dorsomedially to the central nucleus (Faye-Lund and Osen, 1985).

3.2. Neural Inputs to the IC

In mammals, the IC is critical for integration and processing of auditory information. Almost all of the ascending inputs make connections with IC neurons. The IC is the site of termination of almost all LL fibers and the source of axons that ascend through the brachium of the IC to the auditory thalamus (Adams, 1979; Aitkin and Phillips, 1984; Goldberg and Moore, 1967; Morest, 1965). IC not only acts as a relay station, but also receives monaural and binaural inputs from the auditory cortex.

The experiments in which large amount of horseradish peroxidase (HRP) were injected into the ICC have demonstrated that the auditory pathways which diverge from the CN into multiple ascending tracts largely converge in the ICC (Adams, 1979; Brunso-Bechtold et al., 1981; Roth et al., 1978). Such large injections in the cat result in large numbers of labeled neurons in the bilateral LSO, ipsilateral MSO, bilateral DNLL, ipsilateral VNLL, and contralateral DCN. Small numbers of labeled neurons were found in ipsilateral DCN, AVCN and PVCN, ipsilateral medial nucleus of trapezoid body (MNTB), ipsilateral sagulum, contralateral MSO, and bilateral periolivary regions. Similar labeling patterns after large HRP injections into the ICC have also been seen in the rat (Beyerl, 1978; Druga and Syka, 1984).

The projection from the contralateral LSO is not positive to glycine and thought to be an excitatory input (Kelly, 1997). In the cat, it is also suggested that the ipsilateral MSO serves as an excitatory source like the contralateral LSO (Kelly, 1997). Contralateral DCN, AVCN and PVCN are reported to be the major contributors to the excitatory band in the IC (Oliver and Huerta, 1991). However, the axons from the DNLL and ipsilateral LSO are likely inhibitory (Oliver and Huerta, 1991). Many GABAergic neurons in the ipsilateral VNLL are projecting to the IC (Zhang et al., 1998), so the VNLL may be another inhibitory input to the IC (Figure 3).

---- Insert Figure 3 About Here ----

In the cat, the descending projections from the auditory cortex to the ICC are restricted to the dorsomedial division (Andersen et al., 1980; Diamond et al., 1969; Morest and Oliver, 1984; Rockel and Jones, 1973). The descending projections are also confirmed by observations in the mouse (Willard and Ryugo, 1983). However, in the rat, it is reported that the cortical descending projections are to the dorsomedial and ventromedial divisions of the ICC (Beyerl, 1978; Druga and Syka, 1984).

3.3. Intrinsic and Chemical Properties of the IC Neurons

In rat ICC neurons, there are three types of responses to intracellular injection of depolarizing currents. An *in vitro* study (Li et al., 1998) has shown the presence of on, rapidly-adapting, and sustained firing types of neurons in each IC subdivision (ICC, external cortex and dorsal cortex). The sustained firing type was the most common among the three (Li et al., 1998).

The NMDA and non-NMDA receptors were studied in the external nucleus and the lateral nucleus of IC in the barn owl (Feldman and Knudsen, 1994). It is reported that excitatory amino acid receptors mediate most of auditory responses in the external nucleus and lateral shell. NMDA receptors mediate the majority of the auditory responses in the external nucleus, while non-NMDA receptors contribute to the both subdivisions (Feldman and Knudsen, 1994).

GABAergic neurons are also found in the IC (Fubara et al., 1996; Oliver et al., 1994). Glutamic acid decarboxylase (GAD) (synthesizing enzyme for GABA)- or GABA-positive neurons were found in a remarkable population of cells in the ICC, up

to 20% of the ICC neurons in the cat (Oliver et al., 1994). Using GABA_A receptor antagonist, bicuculline, Koch and Grothe (1998) found that GABAergic inhibition sharpened the tuning to frequency modulations in the IC of the big brown bat.

In the big brown bat, glycine receptors were found to be concentrated mainly in the dorsomedial region of the IC, whereas very little labeling was observed in the ventrolateral region (Fubara et al., 1996).

3.4. Physiology of the IC, Emphasis on the ICC

The tonotopic organization of the ICC has been described in a number of species with electrophysiological methods. With electrode penetrations from dorsal to ventral through the ICC in the cat, the characteristic frequencies progressively go higher (Aitkin et al., 1970; Merzenich and Reid, 1974; Rose et al., 1963). A dorsal-to-ventral tonotopic organization has been also found in the rat (Clopton and Winfield, 1973; Flammino and Clopton, 1975; Kelly et al., 1991), rhesus monkey (Ryan and Miller, 1978), rabbit (Aitkin et al., 1972; Syka et al., 1981), brush-tailed possum (Aitkin et al., 1978), mouse (Harnischfeger, 1978), and bat (Jen et al., 1982).

IC plays a very important role in binaural interaction (Flammino and Clopton, 1975; Phillips and Brugge, 1985). Silverman and Clopton (1977) found that in the rat, contralateral and ipsilateral projections from the two ears had opposite effects on unit activity in the IC. The contralateral pathway facilitated unit activity; while the ipsilateral pathway suppressed this activity. Their findings suggest that the binaural information is processed and integrated in the IC (Silverman and Clopton, 1977).

ICC is also involved in some complex information coding processes, such as modulation, pitch, intensity, complex sound spectra and auditory space coding (Ehret, 1997).

4. Long-term Potentiation

4.1. Definition and Biological Significance of Long-term Potentiation

4.1.1. Definition of long-term potentiation

Long-term potentiation (LTP) was first described in hippocampus in 1973 (Bliss and Lomo, 1973), and has been thought of as a possible synaptic mechanism for learning and memory. It is generally accepted that LTP is a long-lasting enhancement of synaptic activation after high frequency stimulation. The high frequency stimulation induces a high level of depolarization on postsynaptic membrane, which causes the remove of Mg^{2+} blockade on the NMDA receptors; therefore, the NMDA receptors are activated and open for Na^+ and Ca^{2+} . The extracellular Ca^{2+} flows into postsynaptic neurons, which causes an intracellular Ca^{2+} concentration increase. This increase leads to a further depolarization and a serial of changes in several intracellular signaling systems (McEachern and Shaw, 1996), which eventually trigger LTP, a prolonged enhancement of synaptic responses for hours or even days.

But, recently, several studies described the exception to this definition. First, it has been found that the NMDA receptors are not required for all kinds of LTP. Three kinds of LTP that are insensitive to the NMDA receptor antagonist APV have been found in addition to the NMDA-dependent LTP in CA1 area of the hippocampus in

the rat (Aniksztejn and Ben-Ari, 1991; Grove and Teyler, 1990a, b; Zalutsky, and Nicoll, 1990). Also, some studies (Bashir and Collingridge, 1994; Larson et al., 1993) suggest that the long-lasting property of LTP is reversible as LTP could be 'depotentiated' after its induction. On the other hand, several procedures other than high frequency stimulation could evoke LTP successfully, such as low frequency stimulation followed by a postsynaptic depolarization (Bindman et al., 1987; Gustafsson et al., 1987; Wigstrom et al., 1986).

4.1.2. Distribution of LTP

LTP was first observed in hippocampus, a structure that is thought to be critical to memory and learning (Zola-Morgan et al., 1986). This naturally leads to the argument that LTP is the synaptic basis for memory and learning. In addition to hippocampus, LTP can be induced in rat and cat visual cortex (Artola and Singer, 1993; Kirkwood and Bear, 1995; Kirkwood et al., 1993; Perkins and Teyler, 1988), cat motor cortex (Baranyi and Szente, 1987), rat pyriform cortex (Stripling and Patneau, 1985), rat amygdala (Chapman and Brown, 1988), guinea pig SC (Miyamoto et al., 1990), cat medial geniculate nucleus (Gerren and Weinberger, 1983), rat dorsal and ventral spinal cord (Pockett and Figurov, 1993; Randic et al., 1993), rat superior cervical ganglion (Burgos et al., 1994), and auditory cortex (Kudoh and Shibuki, 1997). As these areas are concerned with different functions from hippocampus, it seems that LTP may be involved in processes other than learning and memory.

Hosomi et al. (1995) did an *in vivo* study and reported LTP in the IC of rat. Under the administration of the GABA_A receptor antagonist, picrotoxin, tetanic stimulation of 50 Hz for 20 s increased the amplitude of the field potentials in ICC to over 120% of the original level in 10 minutes and this enlargement could maintain for 40 minutes or longer. They suggested the possible role of this long-lasting event in the complex auditory processing and integration in IC (Hosomi et al., 1995).

4.1.3. Relationship of LTP and learning, memory

LTP has been thought to be associated with learning and memory since its discovery. Because it is instantly induced by tetanic stimulation, and has a long-lasting duration and synaptic-specificity, LTP appears to have some of the properties of learning and memory, which also are described as fast initiation and long duration (Malenka, 1994).

Because the NMDA receptor is thought to link to LTP, several studies examined the relationship between NMDA receptor and learning or memory. The antagonists to NMDA receptors could decrease the performance on some tasks requiring learning (Walker and Gold, 1994). Staubli et al. (1989) demonstrated that APV impaired the performance in olfactory discrimination task. These results suggest that NMDA receptors are involved in learning and memory, and also further support the correlation of LTP and learning or memory. However, there is an argument that APV has side-effects on learning so that it could affect the task performance through ways other than LTP (Keith and Rudy, 1990).

Doyere et al. (1993) have examined the correlation of LTP and learning by comparing the potentiation induced by artificial tetanic stimulation with the one by a relatively natural stimulation mimicking the endogenous theta-like activity. They found that high-frequency stimulation of hippocampus-perforant pathway induced an increase in the amplitude of population spikes to about 100% of the control level for 3 days, whereas the natural theta bursting only increased the amplitude of population spikes to 50% for only one day. So they suggested that the potentiation induced by a more 'natural' stimulation might be shorter than that by artificial tetanic stimulation. Like LTP induced by artificial stimulation, the evoked EPSP slopes in the dentate gyrus and the amplitude of population spikes in hippocampus-perforant pathway were increased after classical conditioning learning tasks. These results provide strong evidence for the correlation between LTP and classic conditioning learning (McEachern and Shaw, 1996).

More and more studies use genetic and molecular biology techniques trying to figure out the parallel between LTP and learning or memory. Grant et al. (1992) shown that mice with mutations in *fyn*, a gene encoding a non-receptor tyrosine kinase, could not learn to swim to a hidden platform in the Morris water maze (Grant et al., 1992). They therefore suggested that the tyrosine kinase pathway may strengthen the synaptic plasticity in hippocampus (Grant et al., 1992). The genes encoding metabotropic glutamate receptor 1 (mGluR1), a receptor suggested to be involved in LTP, are also widely studied. For example, the mice with mutations in

gene encoding mGluR1 shown a significant reduction of LTP in which the evoked EPSP slopes increased only 16%, much smaller than 56% in the normal mice.

α -calcium-calmodulin-dependent kinase II (α -CamKII) is another important factor for the protein changes following initiation of the long-lasting increasing process in LTP. It was found that without α -CamKII, mice barely expressed LTP (Silva et al., 1992b) and these mice performed poorly on spatial learning in the Morris water maze task (Silva et al., 1992a). However, Silva et al. (1992a) suggested that α -CamKII was not important for all kinds of learning. The mice without α -CamKII did not express LTP in the hippocampus but could complete a visible platform task (Silva et al., 1992a). These results make the relationship between LTP and learning or memory more complicated.

In summary, there is a strong parallel between LTP and learning or memory (McEachern and Shaw, 1996). But as mentioned by McEachern and Shaw (1996), "The fact is, there is no really compelling evidence one way or the other". The link of LTP and learning or memory has been taken for granted as an assumption in some of the studies for many years. On the other hand, some researchers questioned at what point the accumulated correlations 'prove' the connection, although there might be many results supporting the correlation between LTP and learning or memory (McEachern and Shaw, 1996). Recently, more and more evidence has shown that LTP is related to synaptic modification, abnormal neuronal activities, disinhibition and other processes which are thought having little to do with learning or memory.

Therefore, in a broad perspective, LTP may play a role in the processes of learning and memory, as well as in neuronal plasticity, pathology and neural modification.

4.1.4. LTP: possible roles other than learning and memory

Synaptic plasticity and pathology

LTP is thought to be related to synaptic plasticity. For example, kindling is a model which suggests the correlation between LTP and synaptic alterations (McEachern and Shaw, 1996). Kindling is a phenomenon in which repeated low-intensity (subconvulsive) electrical stimulation of forebrain areas leads to a progressive and permanent amplification of the evoked epileptiform discharge and eventual development of convulsive activity (McIntyre and Plant, 1989; Racine, 1972; Racine and Burnham, 1984). It has been widely accepted as a model for human temporal lobe epilepsy, particularly the secondary generalization of complex partial seizures. Kindling involves a long-lasting change in the properties of neurons and is correlated with changes in the excitatory glutamate and inhibitory GABA neurotransmitter systems (Lauterborn et al., 1993; McIntyre and Racine, 1986; Zafra et al., 1991). Kandel et al. (1991) suggested that the mechanisms underlying kindling might be similar to LTP, in which a brief period of intense activity gives rise to a persistent change in synaptic strength.

Since the mechanism for kindling can be related to LTP, LTP may be linked to pathological changes in neurons. Correlation between LTP and kindling is shown by many studies. First, the similar high frequency stimulation can induce long-term

changes in both cases. Second, for initiation of LTP or kindling, activation of NMDA receptors, and then increase in intracellular Ca^{2+} concentration are required. In addition, some other factors related to LTP, such as mGluR (Akiyama et al., 1992; Bashir et al., 1993), protein kinases (Stevens and Wang, 1994; Suzuki, 1994), genetic changes (Qian et al., 1993) and synthesis of proteins (Bliss and Collingridge, 1993), are also associated with kindling. Also, there is evidence that LTP and kindling have similar morphological changes (Geinisman et al., 1995). Therefore, there is an idea that LTP might be the cellular mechanism for kindling (Baudry, 1986; Collingridge and Bliss, 1987; Slater et al., 1985).

Receptor modifications

It has been shown that LTP is related to receptor homeostasis, regulation and synaptogenesis. In young animals, the depolarizing stimulation can increase the excitatory level of non-NMDA receptors and reduce the binding of GABA_A receptors and thus cause a positive feedback, anti-homeostatic (or 'homeodynamic') state (McEachern and Shaw, 1996). Much more excitation than inhibition occurs as a result of alteration of the balance between excitation and inhibition (Ben-Ari et al., 1988; Cherubini et al., 1990; Swann et al., 1991; Wasterlain and Shirasaka, 1994). This idea is consistent with the mechanism of LTP, by which synaptic activities are boosted to a higher level after tetanic stimulation. The adult neurons appear to have the property to minimize the long-term changes in the synaptic activities, therefore in some cases, LTP is achieved only by depressing the inhibition (Larson and Lynch, 1986). These results suggest that LTP not only serves as a neuronal mechanism for learning and

memory, but also induces the process that raises the neuronal activity level or enhances the possibility of synaptic regulation and modification.

4.2. Relative Factors of LTP

As mentioned above, there are two forms of LTP: NMDA receptor-dependent and NMDA receptor-independent. NMDA receptor mediated LTP requires an increase of postsynaptic intracellular Ca^{2+} concentration through NMDA receptor ion channels and then, an activation of postsynaptic protein kinase, especially protein kinase C (PKC) (Cheng et al., 1994) and CamKII (Aiba et al., 1994a). In addition, cyclic guanosin monophosphate (cGMP) (Hawkins et al., 1994; Zhou et al., 1994) and adenosine triphosphate (ATP) (Wieraszko and Ehrlich, 1994) as second messengers are also required. There is an evidence suggesting that certain subtypes of the mGluR are also involved in the initiation of LTP. LTP was inhibited by blocking mGluR1 in 15-30 day-old and in adult rat hippocampus, and enhanced by applying mGluR1 agonist (Aiba et al., 1994a, b; Gustafsson et al., 1987; Reidel et al., 1994; Richter-Levin et al., 1994). The inhibitory neurotransmitter mechanisms, including GABA_A and GABA_B receptors, seem to play a role in generation of LTP as well. When GABA_A receptors were blocked in adult cat motor cortex, LTP was permitted (Chen et al., 1994). GABA_B receptors could have the facilitating or suppressing effects on LTP. The different effects may be due to the location of the receptors, i.e., presynaptic vs. postsynaptic. The detailed discussion of this point is in the section 4.2.2.

It has been suggested that some other factors are related to LTP. LTP was suppressed by dopamine D2 receptor antagonist in adult rabbit hippocampus (Jibiki et al., 1993). In the study done by Arai et al. (1990), LTP was prevented by applying the agonist of adenosine (A_1) receptors in rat hippocampus. A subtype of serotonin receptor, 5-hydroxytryptamine (3) ($5-HT_3$) receptor, was also indicated to affect LTP (Passani et al., 1994). Recently, several studies focused on the effects of nitric oxide (NO) on LTP. It was found that LTP was abolished by blocking NO synthase (NOS) (Hawkins et al., 1994).

4.2.1. NMDA receptors

There are two different types of glutamate receptors, i.e., ionotropic and metabotropic excitatory glutamate receptors. The ionotropic glutamate receptors have been divided into non-NMDA and NMDA receptors according to their affinities to NMDA. The non-NMDA receptors have been, furthermore, subdivided into 'kainate' and 'AMPA' (formerly 'quisqualate') receptors (Monaghan et al., 1989; Watkins and Evans, 1981).

NMDA receptors have a large single channel conductance (Nowak et al., 1984), a high Ca^{2+}/Na^+ permeability ratio (MacDermott et al., 1986), a voltage-dependent Mg^{2+} blockade (Mayer et al., 1984; Nowak et al., 1984), a high affinity for glutamate, a requirement for glycine as a coagonist (Johnson and Ascher, 1987; Klechner and Dingledine, 1988), and relatively slow activation and deactivation (Jahr,

1992; Johnson and Ascher, 1987; Lester et al., 1990; Lester and Jahr, 1992; Stern et al., 1992).

After the first finding that NMDA receptor is related to initiation of LTP in hippocampus (Collingridge et al., 1983), Collingridge et al. (1983) gave the evidence for the relation between LTP and non-NMDA or NMDA receptors: (i) The non-specific non-NMDA/NMDA receptor antagonist, γ -D-glutamylglycine (DGG), depressed synaptic transmission evoked by low frequency stimulation of the Schaffer collateral-commissural (Sch) pathway of the rat hippocampus. (ii) Blockers, such as APV, for the NMDA receptor-gated ion channel prevented the induction of LTP (Coan et al., 1987; Stringer and Guyenet, 1983). For example, in hippocampus, APV prevented LTP in the perforant pathway input to the dentate gyrus *in vivo* (Errington et al., 1987; Morris et al., 1986) and in the associational/commissural pathway. (iii) APV had no effect on the already potentiated response. (iv) Brief application of NMDA enhanced the synaptic responses (Bashir et al., 1994). By now, the common interpretation of the above results is that low frequency transmission is mediated by the non-NMDA receptors, whereas LTP is triggered by activation of NMDA receptors.

Most of the researchers agree that activation of NMDA receptors is important for induction of LTP, though it is not required for the NMDA-independent LTP. The depolarization caused by tetanic stimulation removes Mg^{2+} ions that block the NMDA receptors at the resting level. And then Ca^{2+} ions enter through the receptors from

extracellular medium, which further activates protein kinases, makes additional release of Ca^{2+} from intracellular stores, and then induces LTP.

4.2.2. GABA_B receptors

To date, three kinds of receptor for GABA, a major inhibitory neurotransmitter in the mammalian central nervous system, have been found: GABA_A, GABA_B and GABA_C receptors. GABA_A receptors are ionotropic and mediate a fast inhibition lasting only for a few milliseconds. It is suggested that GABA_A receptors are directly coupled to an integral chloride channel and produce inhibition by increasing the membrane chloride conductance. This synaptic inhibition is important for maintaining and shaping neuronal communication (Hammond, 1996). GABA_B receptor is thought to be a G-protein coupled, metabotropic receptor. Like other G-protein linked receptors, GABA_B receptor belongs to the family of genes that encode seven transmembrane domain proteins. This receptor has a molecular weight of approximately 80 KDa (Hammond, 1996). There are several signaling pathways linked to the GABA_B receptor. These factors have various effects on pre- and postsynapses. These factors include adenylyl cyclase, inositol triphosphate synthase, voltage-dependent calcium channels and potassium channels.

GABA_B receptors are not affected by bicuculline, but are blocked by GABA_B receptor antagonists which include 3-amino-2-(4-chlorophenyl)propylphosphonic acid (phaclofen), β -(aminomethyl)-4-chloro-benzeneethanesulfonic acid (saclofen), 3-amino-propyl(diethoxymethyl)-phosphinic acid (CGP35348), and 3-*N*[1-(S)-(3,4-

dichlorophenyl]ethyl]amino-2-(S)-hydroxypropyl-*P*-benzyl-phosphinic acid (CGP55845) which is the most potent GABA_B receptor antagonist to date.

GABA_B receptors are found to change with age. In the aged rats, GABA_B receptor binding in the ICC decreased 28% compared with young rats, whereas no significant changes in GABA_A receptor binding were detected (Caspary et al., 1995; Milbrandt et al., 1994). These results may suggest that GABA_B receptors are related to synaptic modification or plasticity.

GABA_B receptors are found to be located presynaptically and postsynaptically. With monoclonal antibodies against GABA_B receptor agonist baclofen, both immunostained terminals and dendrites were observed in several different brain areas, indicating the presence of GABA_B receptors in both the presynaptic and postsynaptic membrane (Hammond, 1996). There is a significant functional difference between pre- and postsynaptic GABA_B receptors (Dutar and Nicoll, 1988; Lambert and Wilson, 1993). Certain presynaptic receptors, called autoreceptors, which are able to recognize and bind the cell's own neurotransmitter, often modulate neurotransmitter release by a feedback mechanism (Kandel et al., 1991). Acting as autoreceptors in presynapses, GABA_B receptors are indicated to reduce the release of GABA, and then, inhibit the effect of postsynaptic GABA_A and GABA_B receptors (Davies and Collingridge, 1996; Pittaluga et al., 1987). Presynaptic GABA_B receptors have been suggested to inhibit different types of voltage-dependent calcium channels, including N-type, P-type, Q-type (Chen and van Den Pol, 1998) and T-type (Hammond, 1996). These inhibitions are thought to be mediated by a G_o protein-coupled process to alter the calcium

channel voltage dependence, which in turn inhibits the release of neurotransmitters, including GABA itself.

Postsynaptic GABA_B receptors, like GABA_A receptors, increase neural inhibition (Connors et al., 1988). These GABA_B receptors activate potassium channels, hyperpolarize the membrane and reduce the input resistance of neurons (Hammond, 1996). It has been shown that the GABA_B receptor-mediated current reverses at the equilibrium for potassium ion. This potassium event has been suggested to be a postsynaptic inhibitory mechanism for GABA_B receptors. The GABA_B receptors are coupled to potassium channels through either one or both of the inhibitory G proteins, G_i and/or G_o (Hammond, 1996).

GABA_B receptors are usually found to co-exist with GABA_A receptors in most regions of the brain. Hammond (1996) shows that GABA_B receptors are less numerous than GABA_A receptors in some regions and equal to GABA_A receptors in other areas of the brain. In the rat central nervous system, GABA_B receptors are about one quarter and one fifth the number of GABA receptors in the dentate gyrus in CA1 and CA3 areas of the hippocampus, respectively. In the hypothalamus, GABA receptors contain 70% GABA_A receptors and 30% GABA_B receptors. In the SC, 65% of GABA receptors are GABA_A and 35% are GABA_B receptors. However, there are a few brain regions, such as some areas in the brainstem and certain thalamic nuclei, where GABA_B receptors can account for up to 90% of the total GABA binding sites (Hammond, 1996).

In the central auditory system of big brown bat, GABA_B receptors are distributed at a low level throughout the subcortical auditory nuclei. However, using [³H]GABA quantitative autoradiography, in the presence of isoguvacine for labeling GABA_B receptors, no [³H]GABA labeling was observed in the nLL, including DNLL, but labeling was most prominent in the dorsomedial part of the IC (Fubara et al., 1996). In the ICC of rat, using the same method, GABA_A receptors were found to account for roughly 78% of total [³H]GABA binding, whereas GABA_B receptors for 22% (Chu et al., 1990).

It is suggested that GABA_B receptor, especially the presynaptic one, is one of the factors that affect LTP (Bowery, 1993). Activation of GABA_B autoreceptors is thought to be necessary to inhibit further GABA release during tetanic stimulation, allowing the depolarization level to reach the threshold for LTP induction (McEachern and Shaw, 1996; Davies et al., 1991). It has been reported that blockade of GABA_B receptors reduces the incidence of LTP in the dentate gyrus. These results suggest that GABA_B receptors inhibit GABA release and then enhance NMDA currents, and, therefore, facilitate LTP (Davies et al., 1991; Davies and Collingridge, 1996; Mott and Lewis, 1991, 1992). Furthermore, the GABA_B receptor agonist could facilitate the development of LTP in the rat dentate gyrus (Mott et al., 1990). Thus, presynaptic GABA_B receptors, like adenosine A₁ and μ -opioid receptors (Scott et al., 1993), seem to serve as the presynaptic inhibition by inhibiting the functional binding of neurotransmitters themselves.

The significance of GABA_B autoreceptors is that they permit activation of NMDA receptors during the brief, high frequency, synchronized discharges, which are thought to occur naturally in the animals. Thus, from a physiological perspective, GABA_B autoreceptor is a key regulator for induction of LTP (Bashir et al., 1994). But there are also some opposite results showing that GABA_B receptor antagonists did not prevent the induction of LTP when long, high frequency trains were delivered (Olpe and Karlsson, 1990; Olpe et al., 1993).

5. Purpose of the Present Study

As mentioned above, Wu and Kelly (1996) reported that NMDA receptors were found in the DNLL neurons of the rat. As the NMDA receptor is critical for at least one type of LTP (NMDA-dependent LTP), the question arises: is it possible to find LTP or LTP-like phenomena in the DNLL. If LTP or LTP-like phenomena could be found in the DNLL, then this would give us another perspective to describe the biological significance of this nucleus. The DNLL is thought to have an important function in binaural information processing. However, no evidence shows that the DNLL is associated with learning, memory or synaptic plasticity. We hypothesized that LTP is unlikely induced in the DNLL (Ma et al., 1999; Zhang and Wu, 1998, 1999). If LTP could be induced, it may have a role other than learning and memory. On the other hand, it has been pointed out that LTP is related to some pathological states, such as kindling and epilepsy (McEachern and Shaw, 1996). It is also possible

that LTP can be induced only under certain abnormal condition, in which the inhibitory influence is removed, for example.

The ICC is an important structure for integration of auditory information and binaural interaction. We hypothesized that it is likely to find LTP or LTP-like phenomena in the ICC. LTP in the ICC might have a significant role in neural plasticity of auditory processing. ICC was reported also to be an origin for the audiogenic seizure (McCown et al., 1984; Wada et al., 1970). This suggests that LTP in the ICC may be associated with the over-excitation and pathological states.

If LTP could be induced in the DNLL but not the ICC or vice versa, it is encouraging to find out what factor is critical for the difference. GABA_B receptor might be a good candidate because there are some GABA_B receptors in the ICC, although not as many as GABA_A receptors, but no significant GABA_B receptors are found in the DNLL (Chu et al., 1990). Furthermore, GABA_B receptors are suggested to make contributions to induction of LTP by inhibiting GABA release from the presynaptic terminals, therefore, disinhibiting postsynaptic neurons and facilitating initiation of LTP (Hammond, 1996).

Materials and Methods

Subject and Slice Preparation

Brain slices were obtained from albino rats (Wistar, Charles River Co., Quebec, Canada) between age of 14 and 35 days old. After they were anesthetized by inhaling halothane, the animals were killed by decapitation. The brains then were removed and submerged in 29-31°C oxygenated normal artificial cerebrospinal fluid (ACSF). The auditory midbrain was blocked, and then sliced at around 400 μm in the frontal plane using a Vibratome tissue slicer. The slice included the ICC, DNLL, LL and CP.

The slice was placed in a recording chamber, sandwiched by two pieces of nylon mesh and perfused by the oxygenated ACSF. The ACSF circulated continuously through the recording chamber and around the brain slice during the entire course of the experiment. The volume of the chamber was about 0.6 ml and the flow rate was kept at 8 to 10 ml/min.

The temperature of the ACSF in the chamber was kept at 30 to 33°C by a heating element. The ACSF consisted of (in mM) 129 NaCl, 3 KCl, 1.2 KH_2PO_4 , 2.4 CaCl_2 , 1.3 MgSO_4 , 20 NaHCO_3 , 3 *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES), and 10 glucose in distilled water, saturated with 95% O_2 -5% CO_2 . The pH was 7.4 after complete saturation with O_2 - CO_2 .

Experimental Protocol

Extracellular Recording

The brain slice was illuminated from below by light passed through a darkfield condenser. The IC, DNLL, CP and LL were visible with a Leitz dissecting microscope. A single recording electrode was inserted into either the ICC or the DNLL. A bipolar stimulating electrode made of insulated tungsten wires with a tip separation of about 50 μm was placed at the ipsilateral DNLL for ICC recording (Figure 4A), and at the LL a few millimeters ventral to the DNLL for DNLL recording (Figure 4B).

---- Insert Figure 4 About Here ----

Glass microelectrodes pulled with a Flaming/Brown micropipette puller (P-80/PC) were used for extracellular recordings. The glass micropipettes were made from 1.0 mm OD and 0.5 mm ID thin-walled glass capillaries with microfilament (Borosilicate with filament, Sutter Instrument Co.). The glass microelectrodes were filled with 3 M sodium chloride. The impedance of the electrodes was 1 to 2 $\text{M}\Omega$. The electrode was lowered by the manipulator into the brain tissue.

Evoked field potentials were recorded with an Axon Instruments Axoprobe 1-A amplifier. The evoked response waveforms were averaged by 5 times and stored with a Nicolet Benchtop Waveform Acquisition System 400.

The test stimulus was 100 μ s in duration presented a rate of 1 every 5 seconds. The baseline control was obtained in response to the test stimulus for at least 20 minutes. To induce LTP or LTP-like responses, a high frequency stimulation (tetanic stimulation), 50 Hz for 20 s, was applied. After the tetanic stimulation, the test stimulus was employed again for at least 30 minutes to examine the long term change in postsynaptic response amplitude and firing pattern. Both test and tetanic stimulation was obtained from a Grass S-8800 stimulator and stimulus isolation unit.

In order to make the excitatory field potentials prominent, 0.5 μ M strychnine (Sigma) and 10 μ M picrotoxin (Sigma) were added to the perfusate during the recording to suppress the glycinergic and GABAergic inhibition, which can also be elicited by electrical stimulation of the LL and CP (Wu and Kelly, 1996). Mg^{2+} -free ACSF was used instead of normal ACSF in the DNLL experiments in order to facilitate induction of LTP by removing blockade of Mg^{2+} on NMDA receptors in the DNLL.

To rule out the possibility of baseline shift by test stimulation, the control group was tested by giving only test stimulation for at least 60 minutes in both DNLL and ICC.

In order to determine the role of NMDA receptors in induction of LTP, the NMDA receptor antagonist APV (Sigma), was applied in the bath 10 minutes before the tetanic stimulation until at least 30 minutes after the tetanic stimulation. The amplitude of the evoked responses was examined continuously before, during and

after application of APV. Then APV was washed out and the same tetanic stimulation was given again. The same protocol was used to study the role of GABA_B receptors in induction of LTP using GABA_B receptor antagonists, phaclofen (Tocris) and CGP35348 (Ciba-Geigy), and GABA_B receptor agonist, baclofen (RBI).

In order to study the effect of GABA_B receptors on induction of LTP via a GABA_A receptor mediated inhibitory mechanism, high concentration picrotoxin (50 μ M) was added to the perfusate to remove most of the GABA_A receptor mediated inhibition. The same protocol of induction of LTP and phaclofen were used for these experiments.

Intracellular Recording

Recording electrodes were made by the same type of micropipettes as for the extracellular recordings mentioned above. The glass microelectrodes were filled with 4 M potassium acetate with the impedance between 100 and 180 M Ω . Once the electrode was positioned over the recording area, it was advanced in 1- μ m steps through the brain slice with a Burleigh piezoelectric driver (Inchworm). An oscillating current (buzzing) was applied to facilitate intracellular penetration.

Intracellular recording was made with an Axon Instruments Axoprobe 1-A amplifier. For recording of synaptic responses from the ICC neurons, the electrical stimulating electrode was placed at the CP medial to the ipsilateral DNLL or of the ipsilateral LL at the DNLL level (Figure 4C). For recording from the DNLL neurons,

electrical stimulation was applied at the CP between the midline and DNLL (Figure 4D).

---- Insert Figure 4 About Here ----

Intracellular current injection was used for examining the cell's input resistance and firing pattern. Data acquisition and current injection protocols were under computer control using Pclamp6 software. The protocol consisted of collecting responses to a series of current pulse (100 ms) between -1 and 1 nA in 0.1 nA steps.

Electrical stimuli were either positive or negative square waves, 100 μ s in duration, obtained from a Grass S-8800 stimulator and delivered through an isolation unit at a repetition rate of one stimulus every one second. The initiation of the stimulation was triggered either by the computer with Pclamp6 software or by the stimulator itself. The synaptic responses were stored with a Nicolet Benchtop Waveform Acquisition System 400 for subsequent analysis.

To obtain GABAergic IPSPs, 0.5 μ M strychnine, 10 μ M CNQX (RBI) or 10 μ M 6,7-dinitroquinoxaline-2,3(1H,4H)-dione (DNQX) (RBI) and 10 μ M APV were used to remove the glycinergic inhibition and glutaminergic excitations, which can be also evoked by stimulation of the LL and CP (Wu and Kelly, 1996).

In order to investigate how GABA_B receptors modulate or mediate GABAergic inhibition, bath application of GABA_B receptor agonist baclofen and antagonists

phaclofen and CGP35348 were used to examine their effects on IPSPs. The cell input resistance was compared before and after application of baclofen. Muscimol (Sigma), a GABA_A receptor agonist, was also be applied for a comparison with baclofen.

Data Analysis

The amplitude of postsynaptic potentials for both extracellular and intracellular recordings was measured from the beginning of the response (baseline) to the peak of the positive or negative waveform. Input resistance was calculated as the ratio of the voltage change to injected current.

Descriptive statistical analysis was done with the Statistics Package of Social Science (SPSS) 6.1 for Windows. Data were expressed as mean and standard error of mean or percentage.

Results

1. LTP in the DNLL and ICC

Long-lasting enhancement of the evoked potentials could be seen in the DNLL after tetanic stimulation with the brain slices in Mg^{2+} - free ACSF containing 0.5 μM strychnine and 10 μM picrotoxin, which suppressed the glycinergic and GABAergic inhibition. Figure 5A shows typical waveforms of the evoked field potentials in a DNLL brain slice before and after tetanic stimulation and after the recovery from the long-lasting enhancement. Figure 5B shows that the amplitude of the evoked potentials was increased to 116.8% of control ($n=13$) in 10 minutes after tetanic stimulation. The increase lasted for at least 30 minutes. In the control group, the slices were tested (Figure 5C) by giving only test stimulation for 90 minutes. Figure 5C shows no amplitude increase in amplitude of the evoked field potentials for these slices ($n=10$). These results rule out the possibility that the test stimulation itself can cause an increase in amplitude of the responses.

---- Insert Figure 5 About Here ----

Figure 6A shows typical waveforms of the evoked field potentials in an ICC brain slice before and after tetanic stimulation and after the recovery from enhancement. The increase in amplitude of the responses was usually larger than that

in the DNLL, but the pattern of the increase in the ICC was similar to that in the DNLL (Figure 6B). The amplitude of the evoked potentials was increased to 136.8% of control (n=63) in 10 minutes after tetanic stimulation, the increase lasted for at least 30 minutes. In some of the slices, such long-term enhancement lasted for several hours until its recovery. The longest enhancement observed in this study lasted for 8 hours and 30 minutes. In the control group, 10 slices were tested to confirm the stability of the baseline. There was no increase in the responses with test stimulation for 90 minutes (Figure 6C).

---- Insert Figure 6 About Here ----

The difference in incidence of LTP between DNLL and ICC was remarkable. LTP was observed in 82.9% of the cases (63 out of 76) in the ICC, but only 30.9% of the cases (13 out of 42) in the DNLL. Furthermore, in 16.7% of the cases in the DNLL the amplitude was decreased after the tetanic stimulation. There was a decrease in only 1.3% cases in the ICC (Figure 7).

---- Insert Figure 7 About Here ----

2. Animal Age and Induction of LTP in the DNLL and ICC

The incidence and amplitude of LTP in the DNLL and ICC were compared between two groups: 14-23 days and 24-35 days. No significant difference in incidence of LTP ($p>0.05$) was found between these two groups in either DNLL or ICC. Also, the percentage of increase in the evoked field potentials after tetanic stimulation did not correlate with animal age in either DNLL or ICC ($p>0.05$). These results suggest that in the present study, animal age (14-35 days) is not a critical factor affecting induction of LTP in the DNLL and ICC.

3. NMDA Receptors and Induction of LTP in the ICC

In order to study components of the evoked field potentials in the ICC, Ca^{2+} -free ACSF was used to examine the synaptic response. As shown in Figure 8B, Ca^{2+} -free ACSF eliminated the second waveform, but not the first one. These results illustrate that the first waveform is a presynaptic response but the second one is a postsynaptic response. The postsynaptic response was totally blocked by DNQX, a non-NMDA receptor antagonist (Figure 8D), but was unaffected by APV, a NMDA receptor antagonist (Figure 8F), which indicates that the postsynaptic response is mediated by non-NMDA receptors but not NMDA receptors.

---- Insert Figure 8 About Here ----

APV prevented induction of LTP effectively in the ICC brain slices. With 20 μM APV in the bath, tetanic stimulation failed to induce LTP (Figure 9B). After APV

was washed out. LTP was observed in the same slice after tetanic stimulation (Figure 9D).

---- Insert Figure 9 About Here ----

A summary of the effect of APV on induction of LTP in the ICC is shown in Figure 10. In 94.7% of the cases (21 out of 24), 20 μ M APV prevented induction of LTP in the ICC. These results indicate that APV could significantly suppress the induction of LTP in the ICC, and further suggest that NMDA receptors are responsible for induction of LTP in the ICC.

---- Insert Figure 10 About Here ----

4. GABA_B Receptors in the DNLL and ICC

4.1. GABA_B Receptors and Induction of LTP in the ICC

The effect of GABA_B receptors was examined with GABA_B receptor antagonists CGP35348 (100 μ M) and phaclofen (200 μ M). Both CGP35348 and phaclofen reversibly prevented induction of LTP in the ICC without affecting the amplitude and pattern of the postsynaptic responses (Figure 11A and 11B). A summary of the effects of phaclofen (n=10) and CGP35348 (n=18) is shown in Figure 12A and 12B, respectively. Phaclofen prevented induction of LTP in 100% of the

cases (10 out of 10) and CGP35348 in 94.4% of the cases (17 out of 18) examined. The results suggest that induction of LTP in the ICC requires an additional activation of GABA_B receptors.

---- Insert Figure 11 About Here ----

---- Insert Figure 12 About Here ----

On the other hand, the GABA_B receptor agonist, baclofen (10 μ M), facilitated induction of LTP in the ICC. In 15 cases, tetanic stimulation was given with the brain slices in ACSF containing baclofen. 93.3% (n=14) of the cases showed a significant amplitude increase (mean=147.8% of baseline). For purpose of comparison, 14 cases were chosen from the normal ACSF group as a control with response baseline level, waveform shape and experimental animal age similar to the baclofen group. Figure 13A shows typical waveforms of the evoked field potentials before and after tetanic stimulation under normal ACSF (upper traces) and baclofen (bottom traces) conditions. Figure 13B shows a comparison of increase in amplitude of the evoked field potentials after tetanic stimulation between baclofen and normal ACSF groups. With baclofen the amplitude of the evoked field potential was increased significantly (Mean $\pm$ SE_{control}=123.84 $\pm$ 3.88%; Mean $\pm$ SE_{baclofen}=147.76 $\pm$ 8.21%, p <0.01, n=14). These results suggest that activation of GABA_B receptors can facilitate induction of LTP in the ICC.

---- Insert Figure 13 About Here ----

In order to examine whether GABA_B receptors play a role in induction of LTP through modulating GABA_A receptors, a high concentration of the GABA_A receptor antagonist, picrotoxin (50 μ M) was added to the bath to block GABA_A receptors totally. Under this condition, phaclofen could not prevent induction of LTP (n=9) (Figure 14). These results demonstrate that if GABA_A receptors are completely blocked, GABA_B receptors will not have any effect on induction of LTP in the ICC. In another words, GABA_B receptors affect induction of LTP through modulating GABA_A receptor mediated inhibition.

---- Insert Figure 14 About Here ----

4.2. GABA_B Receptors in the ICC

Intracellular recordings from ICC neurons were made with the brain slices in ACSF containing 0.5 μ M strychnine, 10 μ M CNQX or DNQX and 10 μ M APV, which suppressed glycinergic IPSPs and glutaminergic EPSPs. IPSPs were recorded in response to stimulation of the CP (Figure 15A). Picrotoxin (10 μ M) abolished the IPSPs completely (n=27), which suggests that the postsynaptic inhibitory response is mediated only by GABA_A receptors (Figure 15B). Among the IPSPs blocked completely by picrotoxin, those in 48.1% cases (n=13) were evoked with stimulation

at the DNLL and all others (n=14) were evoked by stimulation of the CP medial to the DNLL. After application of the GABA_B receptor agonist, baclofen (10 μ M), the amplitude of the IPSP was reduced, but not completely blocked (n=14) (Figure 14D). These results indicate that GABA_B receptors may modulate the GABAergic inhibition in the ICC. Among the IPSPs reduced by baclofen, those in 35.7% of the cases (n=5) were evoked with stimulation at the DNLL, the others (n=9) were evoked by stimulation of the CP medial to the DNLL. No significant effect of 100 μ M CGP35348 (Figure 15 F) and 200 μ M phaclofen (not shown) on the IPSPs was observed, suggesting GABA_B receptors may not make a considerable contribution to GABAergic inhibition in the ICC neurons.

---- Insert Figure 15 About Here ----

Intrinsic membrane properties of the ICC neurons were examined before and after applications of the GABA_A receptor agonist, muscimol (10 μ M), and the GABA_B receptor agonist, baclofen (10 μ M), respectively. Responses to depolarizing and hyperpolarizing currents were recorded by passing currents ranging from -1 or -0.8 nA to 1 nA by 0.1 nA step through intracellular recording electrodes (Figure 16A). The left panel of Figure 16A shows hyperpolarization induced by negative currents, and depolarization and sustaining firing induced by positive currents in normal ACSF. The middle panel of Figure 16A shows decreases in the amplitude of depolarization

and hyperpolarization, and suppression of firing after an application of muscimol (10 μ M) to the bath. The right panel of Figure 16A shows no change in the amplitude of depolarization and hyperpolarization, or action potential firing frequency after an application of baclofen. Current-voltage (I-V) curves were plotted by measuring the membrane potential changes as a function of currents injected (Figure 16B). The cell membrane input resistance was calculated as the ratio of the voltage change to injected current. Muscimol reduced the cell membrane input resistance of the ICC neurons significantly (Mean $\pm$ SE_{control}=65.33 $\pm$ 14.69 M Ω ; Mean $\pm$ SE_{muscimol}=40.38 $\pm$ 13.67 M Ω , p <0.01, n =4) (Figure 16B). These results indicate significant opening of ion channels after activation of GABA_A receptors by muscimol, and large numbers of GABA_A receptors on the postsynaptic membrane in the ICC neurons. In contrast, baclofen did not have a significant effect on cell membrane input resistance of the ICC neurons (Mean $\pm$ SE_{control}=51.28 $\pm$ 7.44 M Ω ; Mean $\pm$ SE_{baclofen}=55.30 $\pm$ 10.60 M Ω , p >0.05, n =12) (Figure 16B). Figure 16C shows that the firing frequencies were roughly the same with the brain slice in normal ACSF or in baclofen. These results suggest that there is no significant postsynaptic effect of GABA_B receptors on the ICC neurons.

---- Insert Figure 16 About Here ----

4.3. GABA_B Receptors in the DNLL

In order to compare the effects of GABA_B receptors on ICC neurons with those on DNLL neurons, intracellular recordings were made from 26 DNLL neurons. IPSPs were recorded from DNLL neurons in response to stimulation of the CP (Figure 17A) with the brain slices in ACSF containing 0.5 μ M strychnine, 10 μ M APV and 10 μ M CNQX or DNQX. As in the case of the ICC neurons, the IPSPs were blocked completely by 10 μ M picrotoxin (n=4) (Figure 17B). However, unlike those in the ICC neurons, the IPSPs were not affected by the GABA_B receptor agonist, baclofen (n=6) (Figure 17D). After bath application of 100 μ M CGP35348 (Figure 17F) and 200 μ M phaclofen (not shown), no significant effect on IPSPs was observed in the DNLL neurons (n=8 for CGP35348; n=1 for phaclofen). These results suggest that the IPSPs in the DNLL neurons are mediated by GABA_A receptors, but not modulated by GABA_B receptors.

---- Insert Figure 17 About Here ----

Intrinsic membrane properties of the DNLL neurons were also examined before and after application of the GABA_A receptor agonist, muscimol (10 μ M), and the GABA_B receptor agonist, baclofen (10 μ M). Responses to depolarizing and hyperpolarizing currents were recorded by passing currents ranging from -1 or -0.8 nA to 1 nA by 0.1 nA step through intracellular recording electrodes (Figure 18A). The left panel of Figure 18A shows hyperpolarization induced by negative currents.

depolarization and sustained firing induced by positive currents in normal ACSF. The middle panel of Figure 18A shows decreases in the amplitude of depolarization and hyperpolarization, and suppression of firing with an application of muscimol. The right panel of Figure 18A shows no change in the amplitude of depolarization and hyperpolarization, or action potential firing frequency with an application of baclofen. I-V curves were plotted and cell membrane input resistance was calculated in the same way as for the ICC neurons (Figure 18B). Muscimol effectively reduced the cell membrane input resistance in one DNLL neuron ($R_{\text{control}}=60.8 \text{ M}\Omega$; $R_{\text{muscimol}}=27.0 \text{ M}\Omega$) (Figure 18B). In contrast, baclofen did not have a significant effect on cell membrane input resistance of the DNLL neurons ($\text{Mean} \pm \text{SE}_{\text{control}}=42.87 \pm 7.78 \text{ M}\Omega$; $\text{Mean} \pm \text{SE}_{\text{baclofen}}=45.47 \pm 8.17 \text{ M}\Omega$, $p>0.05$, $n=6$) (Figure 18B). Figure 18C shows that the firing frequencies were roughly the same with the brain slice in normal ACSF or in baclofen. These results indicate significant opening of ion channels on the DNLL neurons after activation of GABA_A receptors by muscimol, but no manifest effect of activation of GABA_B receptors on the DNLL neurons by baclofen.

---- Insert Figure 18 About Here ----

The effects of the NMDA receptor antagonist (APV), the GABA_B receptor antagonists (phaclofen and CGP35348), the GABA_B receptor agonist (baclofen), the GABA_A receptor antagonist (picrotoxin) and GABA_A receptor agonist (muscimol) on

induction of LTP and/or IPSPs, cell membrane input resistance and action potential firing frequency are summarized in Table 1.

---- Insert Table 1 About Here ----

Figure 1. Photomicrograph of a cresyl violet-stained frontal section through the midbrain and lateral lemniscus. Scale bar: 500 μ m. From Wu (1999).

Figure 2. Highly schematic diagram of major auditory inputs to the DNLL. Open triangle: excitatory input. **Solid triangle:** inhibitory input. **Question mark:** property of input remains unknown.

Figure 3. Highly schematic diagram of major auditory inputs to the ICC. Open triangle: excitatory input. Solid triangle: inhibitory input.

A.

Extracellular recording for ICC

B.

Extracellular recording for DNLL

C.

Intracellular recording for ICC

D.

Intracellular recording for DNLL

Figure 4. Stimulating and recording sites of extracellular and intracellular recordings in the DNLL and ICC. (A) Extracellular recording from the ICC. **(B)** Extracellular recording from the DNLL. **(C)** Intracellular recording from the ICC. **(D)** Intracellular recording from the DNLL. **S:** stimulating electrode. **R:** recording electrode.

B. LTP in the DNLL

C. Control Group in the DNLL

Figure 5. LTP in the DNLL. (A) A typical long-term potentiation of the evoked field potentials recorded from a DNLL brain slice. **Before:** control response indicated with open dot. **After:** potentiated response recorded 375 minutes after tetanic stimulation. **Recovery:** response recorded 525 minutes after tetanic stimulation. **Arrow:** stimulus artifacts. Each trace is an average of 5 individual responses. **(B)** A summary of LTP in the DNLL. The average increase in the amplitude of evoked field potentials was 116.8% of control after tetanic stimulation. **Arrow:** the time for tetanic stimulation. Each data point represents mean $\pm$ SE (n=13). **(C)** A summary of the evoked field potentials to test stimulation for 90 minutes in 10 DNLL slices.

B. LTP in the ICC

C. Control Group in the ICC

Figure 6. LTP in the ICC. (A) A typical long-term potentiation of the evoked field potentials recorded from an ICC brain slice. **Before:** control response indicated with open dot. **After:** potentiated response recorded 40 minutes after tetanic stimulation. **Recovery:** response recorded 60 minutes after tetanic stimulation. **Arrow:** stimulus artifacts. Each trace is an average of 5 individual responses. **(B)** A summary of LTP in the ICC. The average increase in the amplitude of the evoked field potentials was 136.8% of control after tetanic stimulation. **Arrow:** the time for tetanic stimulation. Each data point represents mean $\pm$ SE (n=63). **(C)** A summary of the evoked field potentials to test stimulation for 90 minutes in 10 ICC slices.

Changes in Amplitude of Evoked Field Potentials

Figure 7. A comparison of incidence of increase, unchanged and decrease of the evoked field potential amplitude after tetanic stimulation between DNLL and ICC.

A. Control

B. 0 Ca^{++}

C. Wash

D. 20 μM DNQX

E. Wash

F. 20 μM APV

G. Wash

0.2 mV
2 ms

Figure 8. The evoked field potential in the ICC consists of pre- and postsynaptic components. (A) A field potential with two negative waveforms was evoked with a brain slice in normal ACSF. (B) With the brain slice in Ca^{2+} -free ACSF, the second waveform was abolished whereas the first waveform was unchanged. (C) The postsynaptic response returned after washing the slice with normal ACSF. (D) The postsynaptic response was blocked by 20 μM DNQX. (E) The postsynaptic response recovered after washing with normal ACSF. (F) The postsynaptic response was not affected by 20 μM APV. (G) The postsynaptic response recovered after washing with normal ACSF. **Arrow:** stimulus artifact. **Open dot:** postsynaptic response. **Solid dot:** presynaptic response. Each trace is an average of 5 individual responses.

A. Control

B. After tetanic stimulation
(in 20 μ M APV)

C. Wash

D. After tetanic stimulation
(in normal saline)

Figure 9. APV prevents induction of LTP in the ICC. (A) A field potential with two negative waveforms was evoked in the ICC with a brain slice in normal ACSF. (B) During an application of 20 μ M APV the potential was unchanged for 30 minutes after tetanic stimulation. (C) The response remained the same after washing with normal ACSF. (D) The postsynaptic response was increased after tetanic stimulation with the brain slice in normal ACSF. This field potential was recorded 75 minutes after tetanic stimulation. **Arrow:** stimulus artifact. **Open dot:** postsynaptic response. **Solid dot:** presynaptic response. Each trace is an average of 5 individual responses.

Effect of APV on LTP in the ICC

Figure 10. A summary of the effect of APV on induction of LTP in the ICC.

Arrow: the time for tetanic stimulation. Each data point represents mean $\pm$ SE (n=21).

0.2 mV
2 ms

1 mV
2 ms

Figure 11. CGP35348 and phaclofen prevent induction of LTP in the ICC. (A1) A field potential with two negative waveforms was evoked in the ICC with a brain slice in normal ACSF. (A2) The response did not change after bath application of 100 μ M CGP35348. (A3) During application of CGP35348 the potential was unchanged for 30 minutes after tetanic stimulation. (A4) The response remained the same after washing with normal ACSF. (A5) The postsynaptic response was increased after tetanic stimulation with the brain slice in normal ACSF. This field potential was recorded 30 minutes after tetanic stimulation. (B1) A field potential with two negative waveforms was evoked in the ICC with another brain slice in normal ACSF. (B2) The response did not change after bath application of 200 μ M phaclofen. (B3) During application of phaclofen the potential was unchanged for 30 minutes after tetanic stimulation. (B4) The response remained the same after washing with normal ACSF. (B5) The postsynaptic response was increased after tetanic stimulation with the brain slice in normal ACSF. This field potential was recorded 40 minutes after tetanic stimulation. **Arrow:** stimulus artifact. **Open dot:** postsynaptic response. **Solid dot:** presynaptic response. Each trace is an average of 5 individual responses.

A. Effect of Phaclofen on LTP in the ICC

B. Effect of CGP35348 on LTP in the ICC

Figure 12. A summary of the effects of CGP35348 and phaclofen on induction of LTP in the ICC. (A) Phaclofen prevented induction of LTP (n=10). **(B)** CGP35348 prevented induction of LTP (n=18). **Arrow:** the time for tetanic stimulation. Each data point represents mean $\pm$ SE.

A. Control

Baclofen

B.

Effect of Baclofen on LTP in the ICC

Figure 13. Effect of baclofen on LTP in the ICC. (A) Potentiated responses in normal ACSF and baclofen. **Top traces:** in normal ACSF, the evoked field potential waveforms before and 30 minutes after tetanic stimulation. **Bottom traces:** with 10 μ M baclofen in ACSF, the evoked field potential waveforms before and 30 minutes after tetanic stimulation. **Arrow:** stimulus artifact. **Open dot:** postsynaptic response. **Solid dot:** presynaptic response. Each trace is an average of 5 individual responses. **(B)** A comparison of amplitude increase of LTP in normal ACSF and baclofen in the ICC (n=14). Each bar represents mean+SE. *: p<0.01.

Effect of Phaclofen on LTP in the ICC

Figure 14. Phaclofen failed to prevent LTP in the ICC with the brain slices in high concentration picrotoxin (50 μ M). Arrow: the time for tetanic stimulation.
Each data point represents mean $\pm$ SE (n=10).

10 mV
5 ms

Figure 15. Effects of picrotoxin, baclofen and CGP35348 on IPSPs of an ICC neuron. (A) An IPSP recorded from an ICC neuron in normal ACSF. (B) Picrotoxin (10 μ M) completely blocked the IPSP. (C) The IPSP recovered after washing with normal ACSF. (D) Baclofen (10 μ M) reduced the amplitude of IPSP. (E) The IPSP recovered after washing with normal ACSF. (F) The IPSP was unchanged after an application 100 μ M CGP35348. (G) The IPSP remained the same after washing with normal ACSF. **Arrow:** stimulus artifact.

B.

C.

Figure 16. Effects of muscimol and baclofen on intrinsic membrane properties of an ICC neuron. (A) Left panel: Responses to intracellular injection of 0.6, 0.3, -0.4 and -0.7 pA currents for 120 ms (from the top to bottom traces). **Middle panel:** Responses to intracellular injection of 0.6, 0.3, -0.4 and -0.7 pA currents for 120 ms (from the top to bottom traces) with the slice in 10 μ M muscimol. **Right panel:** Responses to intracellular injection of 0.6, 0.3, -0.4 and -0.7 pA currents for 120 ms (from the top to bottom traces) with the slice in 10 μ M baclofen. **(B)** I-V curves obtained by plotting cell membrane potential changes as a function of each current injected into this neuron with the slice in normal ACSF, muscimol and baclofen. **(C)** Firing frequency as a function of the strength of positive currents injected into this neuron with the slice in normal ACSF and baclofen.

10 mV
5 ms

Figure 17. Effects of picrotoxin, baclofen and CGP35348 on IPSPs of a DNLL neuron. (A) An IPSP recorded from a DNLL neuron in normal ACSF. (B) Picrotoxin (10 μ M) completely blocked the IPSP. (C) The IPSP recovered after washing with normal ACSF. (D) The IPSP was unchanged after an application of 10 μ M baclofen. (E) The IPSP remained the same after washing with normal ACSF. (F) The IPSP was unchanged after an application 100 μ M CGP35348. (G) The IPSP remained the same after washing with normal ACSF. **Arrow:** stimulus artifact.

B.

C.

Figure 18. Effects of muscimol and baclofen on intrinsic membrane properties of a DNLL neuron. (A) **Left panel:** Responses to intracellular injection of 1.0, 0.6, -0.3 and -0.6 pA currents for 180 ms (from the top to bottom traces). **Middle panel:** Responses to intracellular injection of 1.0, 0.6, -0.3 and -0.6 pA currents for 180 ms (from the top to bottom traces) with the slice in 10 μ M muscimol. **Right panel:** Responses to intracellular injection of 1.0, 0.6, -0.3 and -0.6 pA currents for 180 ms (from the top to bottom traces) with the slice in 10 μ M baclofen. (B) I-V curves obtained by plotting cell membrane potential changes as a function of each current injected into this neuron with the slice in normal ACSF, muscimol and baclofen. (C) Firing frequency as a function of the strength of positive currents injected into this neuron with the slice in normal ACSF and baclofen.

Table 1. A Summary of Effects of APV, Phaclofen, CGP35348, Baclofen, Picrotoxin and Muscimol on Induction of LTP and/or IPSPs, Cell Membrane Input Resistance and Action Potential Firing Frequency in the DNLL and ICC

	APV NMDA Receptor Antagonist	Phaclofen GABA _B Receptor Antagonist	CGP35348 GABA _B Receptor Antagonist	Baclofen GABA _B Receptor Agonist	Picrotoxin GABA _A Receptor Antagonist	Muscimol GABA _A Receptor Agonist
Concentration (μ M)	20	200	100	10	10 50	10
Effect on Induction of LTP	Block	Block	Block	Facilitate	-	-
Effect on IPSPs in the DNLL Neurons	-	No Change	No Change	No Change	Block	-
Effect on IPSPs in the ICC Neurons	-	No Change	No Change	Reduce	Block	-
Effect on Cell Membrane Input Resistance in the DNLL Neurons	-	-	-	No Change	-	Reduce
Effect on Cell Membrane Input Resistance in the ICC Neurons	-	-	-	No Change	-	Reduce
Effect on Action Potential Firing Frequency in the DNLL Neurons	-	-	-	No Change	-	Reduce
Effect on Action Potential Firing Frequency in the ICC Neurons	-	-	-	No Change	-	Reduce

Discussion

1. LTP in the DNLL and ICC

In the present study, LTP was induced in both DNLL and ICC by tetanic stimulation (50 Hz for 20 s) with the brain slices in ACSF containing 0.5 μ M strychnine and 10 μ M picrotoxin, which suppressed the glycinergic and GABAergic inhibition. The patterns of the long-lasting enhancement in the DNLL and ICC were similar. Usually, the gradual increase of the evoked field potential was observed in 10 minutes after tetanic stimulation, and the increase lasted for at least 30 minutes. These results are consistent with the observation that LTP could be induced in the ICC *in vivo* using the tetanic stimulation with similar parameters (Hosomi et al., 1995). These results together suggest that long-lasting information processing and synaptic transmission could happen in both DNLL and ICC.

The correlations between experimental animal age (14-35 days) and incidence/amplitude of LTP were not significant in either DNLL or ICC. It is reported that the optimal age for induction of LTP in rat hippocampus is 15 days old (Harris and Teyler, 1984). But no such trend is shown in the present study, which suggests that the animal's age used in this study is not a critical factor for induction of LTP in the DNLL and ICC under the present conditions.

However, the difference in incidence of LTP in the DNLL (30.9%) and ICC (85.5%) is significant. The amplitude of the evoked field potentials stayed unchanged

in 52.4% of the cases in the DNLL, but in only 15.8% of the cases in the ICC. The decrease of the amplitude after tetanic stimulation happened in 16.7% cases in the DNLL, but in only 1.3% of the cases in the ICC. The increase in amplitude of the evoked field potentials in the DNLL slices was smaller than that in the ICC slices (16.8% versus 36.8%). All these data indicate that LTP can not be readily induced in the DNLL, and that the LTP that was developed in around 1/3 of the DNLL slices was also much less noticeable than that in the some other areas of the central nervous system (CNS), such as the SC (Miyamoto et al., 1990), medial geniculate nucleus (Gerren and Weinberger, 1983), dorsal (Randic et al., 1993) and ventral spinal cord (Pockett and Figurov, 1993). In these structures the amplitude of LTP is at least 120% of the control. In contrast, LTP can be easily induced in the ICC using a method of tetanic stimulation similar to that used for LTP induction in the hippocampus (Bliss and Collingridge, 1993), visual cortex (Bear and Kirkwood, 1993), SC (Miyamoto et al., 1990) and ICC *in vivo* (Hosomi et al., 1995). The extent of the increase in amplitude of the evoked field potentials in the ICC in this study was also comparable to that in other regions of the brain (Gerren and Weinberger, 1983; Hosomi et al., 1995; Miyamoto, et al., 1990).

The differences in LTP between DNLL and ICC may be explained by different roles of the DNLL and ICC in auditory information processing. Electrophysiological and behavioral studies have shown that the DNLL serves in binaural processing and sound localization (Kelly, 1997), which depend on binaural cues, i.e. interaural time and intensity differences. Binaural processing that requires relatively fast synaptic

interactions to accomplish neuronal computation may not depend on long-lasting enhancement of synaptic transmission in the DNLL. However, it has been thought that LTP is one of the cellular mechanisms for learning and memory. But until now, no evidence supports the idea that DNLL plays a role in learning, memory and any forms of synaptic plasticity.

A activation of NMDA receptors is necessary for induction of LTP (Barrioneuve and Brown, 1983; Ben-Ari et al., 1992; Bliss and Collingridge, 1993; Dunwiddie and Lynch, 1978; Madison et al., 1991; Malenka, 1994). Intracellular and whole-cell patch clamp recordings from rat's DNLL neurons show the presence of NMDA receptors there. Excitatory synaptic transmission in the DNLL is mediated by both NMDA and non-NMDA receptors (Wu and Kelly, 1996; Fu et al., 1997). The basic properties, including kinetics, voltage dependence and pharmacology of NMDA receptors in DNLL neurons, are similar to those in other CNS neurons, including hippocampal and auditory neurons (Forsythe and Westbrook, 1988; Hestrin et al., 1990; Forsythe and Barnes-Davies, 1993; Zhang and Trussell, 1994). NMDA receptors are activated only when neurons are depolarized because the depolarization removes Mg^{2+} blockade on NMDA receptors. To avoid the possibility that Mg^{2+} blockade on the NMDA receptor would prevent LTP, all experiments for testing LTP in the DNLL in this study were conducted with the brain slice in Mg^{2+} -free ACSF. Thus, the results that show a much lower incidence and degree of LTP in the DNLL compared to those in the ICC certainly are not attributable to Mg^{2+} blockade on NMDA receptors. In addition, the evoked field potential of the DNLL is rather small.

Whether or not the weak LTP in the DNLL is due to the small field potential is not clear. Further study using intracellular or whole cell patch clamp recording instead of extracellular recording to examine long term modification on EPSPs of DNLL neurons is certainly required for investigation of neuronal plasticity in the DNLL.

The mechanisms of development of LTP in the CNS are still not completely understood. Various factors including presynaptic and postsynaptic events are involved. At this stage, it is difficult to determine what causes the difference in induction of LTP in the DNLL and ICC. However, one factor, the presence of the GABA_B receptor, may be responsible for this difference (see discussion 3).

The ICC in the rat is thought to be a midbrain relay station that integrates almost all the information from the lower auditory nuclei. The ICC is suggested to be involved in many complex auditory information coding processes, such as processing modulated sound, pitch, sound intensity, complex sound spectra and auditory space (Ehret, 1997). These complicated processes happening in the ICC might require a long-lasting excitation and/or inhibition, or a relatively strong synaptic transmission, which would provide enough transmission time and intensity to extract large amounts of detailed information. Besides the roles in auditory function, the ICC is also suggested to make contributions to various processes, such as acoustic input learning/memory and audiogenic seizure (Hosomi et al., 1995), which are thought to be linked to synaptic plasticity and neuronal pathology. LTP in the ICC may be involved in these processes.

The discovery of LTP in the auditory system is intriguing because it questions whether LTP is a mechanism of learning and memory and furthermore, what the biological significance of LTP is in the auditory system. There is much evidence supporting the parallel between LTP and learning or memory (McEachern and Shaw, 1996). But as mentioned by McEachern and Shaw (1996), "The fact is, there is no really compelling evidence one way or the other". The link of LTP and learning or memory has been taken for granted as an assumption in some of the studies for many years. On the other hand, some researchers questioned at what point the accumulated correlations 'prove' the connection, although there might be many results supporting the correlation between LTP and learning or memory (McEachern and Shaw, 1996). As we discussed above, although the possibility that the ICC is involved in learning and memory could not be ruled out, a likely explanation for the LTP found in the ICC is that LTP might have roles other than learning and memory. Recently, more and more evidence has shown that LTP is related to synaptic modification, abnormal neuronal activities, disinhibition and other processes, which have little to do with learning or memory. Therefore, in a broad perspective, LTP may play a role in processes of learning and memory, as well as in neuronal plasticity, pathology, neuronal modification and complex information processing.

2. NMDA Receptors and Induction of LTP in the ICC

In this study, APV, a NMDA receptor antagonist, effectively and reversibly blocked induction of LTP in the ICC, which suggests a requirement of activation of

NMDA receptors for induction of LTP in the ICC. The NMDA receptor dependent LTP is observed in many areas of brain and is by far the type most discussed in the literature. It is also reported that NMDA receptors are required for induction of LTP in the adult cat motor cortex (Baranyi and Szente, 1987), rat and cat visual cortex (Artola and Singer, 1987; Kirkwood and Bear, 1994; Kirkwood et al., 1993; Perkins and Teyler, 1988) and rat amygdala (Chapman and Brown, 1988). As found in the hippocampus, neocortex and some other areas of the brain, the dependence on NMDA receptors is one of the most important requirements for the LTP in the ICC. When tetanic stimulation induces a large enough depolarization at postsynaptic neurons, the blockade of Mg^{2+} will be removed and then NMDA receptor ion channels will be opened. Ca^{2+} will flow into the postsynaptic membrane and cause further depolarization, which will open more NMDA receptors. This positive loop keeps the postsynaptic neurons depolarized for a relatively long time, resulting in the induction of LTP. The voltage-dependent blockade of Mg^{2+} makes NMDA receptors work as a molecular coincidence detector (Bliss and Collingridge, 1993). In order to open NMDA receptor ion channels, it is required that two events happen together: enough depolarization of the postsynaptic membrane and opening of the NMDA receptor channels by binding glutamate to NMDA receptors. The cellular mechanism of dependence of NMDA receptors for generation of LTP in the ICC is very likely the same as that in other regions of the brain.

3. GABA_B Receptors and Induction of LTP in the ICC and DNLL

3.1. GABAergic System and LTP

The GABAergic system is known to participate in auditory processing in the ICC. Neuroanatomical and immunochemical studies suggest that there are GABAergic inputs to the ICC from the ipsilateral VNLL, and ipsilateral and contralateral DNLL (González-Hernández et al., 1996; Zhang et al., 1998). It is also reported that within the IC there are many interneurons that are GABA-positive as defined by immunoreactivities to GAD (Fubara et al., 1996; Oliver et al., 1994). In normal physiological situation, GABAergic inhibition has the effect of suppressing long-term excitation (Park and Pollak, 1993; Pollak, 1997), which can last for hundreds of milliseconds after removal of GABAergic inhibition (Zhang et al., 1999). In this study, stimulating the LL ventral to the ICC probably activated the GABAergic inputs from the ipsilateral VNLL and DNLL, as well as contralateral DNLL and interneurons within the ICC. In order to facilitate induction of LTP, the GABA_A receptor antagonist, picrotoxin (10 μ M), was added to the perfusate to suppress the GABAergic inhibition. LTP was then easily induced in the ICC under this condition. Similarly, induction of LTP would be possible only when GABAergic inhibition is removed or reduced by GABA_A receptor inhibitors in neocortex (Hirsch and Crepel, 1990; Kirkwood and Bear, 1994), ICC *in vivo* (Hosomi et al., 1995), motor cortex (Chen et al., 1994) and visual cortex (Kirkwood and Bear, 1994). However, it is not clear whether LTP could be induced in the ICC with GABAergic inhibition intact and how much the GABAergic inhibition modifies induction of LTP. Further studies are

needed to answer questions regarding the interaction between excitation and inhibition in the ICC.

3.2. GABA_B Receptors and Induction of LTP

Induction of LTP is subject to the factors that modify the level of depolarization during tetanic stimulation. Synaptic inhibition is one of these factors (Mott and Lewis, 1992). It has been reported that activation of GABA_B receptors can suppress GABAergic inhibition (Deisz and Prince, 1989; Mott and Lewis, 1992). However, the mechanism of this disinhibition is not very clear. One possible explanation is that GABA_B receptors shunt or suppress the GABA_A receptor-mediated IPSPs by reducing the amount of synaptically released GABA. Thus, the disinhibition enhances the NMDA receptor-mediated component of the response during tetanic stimulation, triggering LTP.

In the present study, the GABA_B receptor antagonists, CGP35348 and phaclofen, effectively blocked induction of LTP in the ICC. This is consistent with the results from the dentate gyrus in the hippocampus where GABA_B receptor-mediated disinhibition is required for induction of LTP (Mott and Lewis, 1992). On the other hand, the results from this study show that the GABA_B receptor agonist, baclofen, facilitated induction of LTP in the ICC. Not only was the incidence of LTP higher (93.3% versus 85.5%), but also the amplitude of the potentiated response was larger (123.84% versus 147.76% of control) with the brain slice in baclofen than in normal ACSF. A similar and even more robust effect of baclofen on LTP has been reported in

the dentate gyrus of the hippocampus (Mott et al., 1990). The suppression effect by the GABA_B receptor antagonist and facilitation effect by the GABA_B receptor agonist on LTP in the ICC support the concept that activation of GABA_B receptor is a requirement for induction of LTP in addition to NMDA receptor. Several studies have also illustrated the critical role of GABA_B receptor-mediated disinhibition in development of LTP in CA1 (Davies et al., 1991) and CA3 (Thompson and Gähwiler, 1989) areas of the hippocampus, and the neocortex (Deisz and Prince, 1989).

3.3. Possible Mechanisms of GABA_B Receptors

GABA_B receptors could reduce the GABA release from the GABAergic terminals through a presynaptic mechanism (Mott and Lewis, 1992). Harrison (1990) recorded inhibitory postsynaptic currents (IPSCs) from the cultured hippocampus neurons. Application of baclofen suppressed the IPSC without hyperpolarizing the neuron that was being recorded from. The author suggested that the reduction of the IPSC by baclofen may be due to suppressing GABA release. In addition, several studies using crude synaptosomal preparations from the rat median eminence (Anderson and Mitchell, 1985), substantia nigra (Giralt et al., 1990), cerebral cortex (Bonanno et al., 1989b; Pittaluga et al., 1987), and human cerebral cortex (Bonanno et al., 1989a) have demonstrated that both GABA and baclofen can inhibit potassium-evoked, Ca²⁺-dependent [³H]GABA release through activation of presynaptic GABA_B autoreceptors.

In the present study, the IPSPs of ICC neurons were completely blocked by picrotoxin, but not affected at all by phaclofen and CGP35348. These results indicate that the IPSPs are mediated only by GABA_A receptors. However, the GABA_B receptor agonist, baclofen, reduced the amplitude of the IPSPs in the ICC neurons, indicating that baclofen activates GABA_B receptors which may be present on presynaptic site, because baclofen can inhibit GABA release and suppress postsynaptic inhibitory responses by activating presynaptic GABA_B autoreceptors (Bashir et al., 1994; Davies et al., 1991; Mott et al., 1990).

The effects of baclofen on cell membrane properties of the ICC neurons provide further evidence of the location of GABA_B receptors in the ICC. Application of baclofen did not affect the cell membrane input resistance or action potential firing frequency as measured from responses to intracellular injection of hyperpolarizing and depolarizing currents. In contrast, GABA_A receptor agonist, muscimol, decreased the cell membrane input resistance and firing rate dramatically. These results clearly demonstrate the lack of postsynaptic GABA_B receptors and the presence of GABA_A receptors on the postsynaptic cell membrane, in which ion channels can be opened and membrane conductance, in turn, decreased by muscimol.

Intracellular recordings from DNLL neurons in the present study showed neither pre- nor postsynaptic GABA_B receptor actions. Similar to those in the ICC neurons, the IPSPs in the DNLL neurons were completely eliminated by picrotoxin, but not affected by phaclofen and CGP35348, suggesting that the IPSPs were mediated by GABA_A receptors totally. However, unlike those in the ICC neurons, the

amplitude of the IPSPs were not changed by application of baclofen. Also, similar to the ICC neurons, DNLL neurons were very sensitive to the GABA_A receptor agonist, muscimol, which reduced the cell membrane input resistance and action potential firing frequency significantly, but were not sensitive at all to baclofen. These results imply the presence of large numbers of postsynaptic GABA_A receptors, but few of either pre- or postsynaptic GABA_B receptors in the DNLL neurons. These physiological results from the DNLL and ICC are consistent with the evidence from autoradiographic studies showing little GABA_B receptor labeling in the nLL, including DNLL, but some labeling in the ICC (Fubara et al., 1996; Chu et al., 1990).

In order to confirm that GABA_B receptors may modulate GABA release and exert an effect on induction of LTP via GABA_A receptors in the ICC, a high concentration picrotoxin (50 μ M) was added to the bath to completely block GABA_A receptors. Under this condition, phaclofen failed to prevent induction of LTP in the ICC. These results suggest that LTP can not be prevented because of complete suppression of GABA_A inhibition. In other words, LTP can be generated when GABA_B receptors are activated, only if there is a corresponding reduction of GABA release and suppressing GABAergic inhibition through GABA_A receptors. If GABA_A receptors are blocked, the modifying effect of GABA_B receptors on GABA_A inhibition will not occur. In the present study, electrical stimulation of the LL at the site of DNLL area in the brain slice probably activated most GABAergic inputs to the ICC, which include the collateral axons of the CP that arise from the contralateral DNLL, the DNLL neurons that project ipsilaterally to the ICC, ipsilateral VNLL and

interneurons within the ICC (Adams and Mugaini, 1984; Moore and Moore, 1987; Roberts and Ribak, 1987; Shneiderman et al., 1993). Activation of GABA_B receptors may modify these GABAergic inputs during tetanic stimulation, and then in turn, result in development of LTP.

The effect of GABA_B receptors on induction of LTP via GABA_A receptor mediated inhibition in the ICC can also explain the low incidence of LTP in the DNLL. Because no evidence shows GABAergic inputs to the DNLL through the LL or the presence of GABAergic interneurons within the DNLL (Wu and Kelly, 1995a, b, 1996), stimulating the LL ventral to the DNLL may not activate any GABAergic inhibition to the DNLL. Thus, the modifying effect of GABA_B receptors on GABA release, GABAergic inhibition and induction of LTP would not be possible even if GABA_B receptors did exist on presynaptic terminals of the GABAergic inputs to the DNLL neurons.

In summary, the above results about GABA_B receptors suggest that presynaptic GABA_B receptors are important for induction of LTP in the ICC. LTP was induced in the ICC and blockade of GABA_B receptors prevented induction of LTP in the ICC, where presynaptic modulating effects of GABA_B receptors were detected by intracellular recordings. LTP was only weakly induced in the DNLL where action of GABA_B receptors was not observed physiologically.

Conclusions

Long-term potentiation (LTP) can be induced in both DNLL and ICC with tetanic stimulation (50 Hz, for 20 seconds) of the lateral lemniscus. The incidence and amplitude of LTP are significantly greater in the ICC than in the DNLL, suggesting the different functional significance and mechanism of LTP in the DNLL and ICC.

The potentiated field responses in the ICC can be completely blocked by the non-NMDA receptor antagonists, CNQX and DNQX, but are not affected by the NMDA receptor antagonist, APV. These results suggest that the expression of LTP in the ICC is mediated by non-NMDA receptors, but not NMDA receptors.

Induction of LTP in the ICC can be reversibly prevented by the NMDA receptor antagonist, APV, suggesting that induction of LTP in the ICC requires the activation of NMDA receptors. Induction of LTP in the ICC can also be reversibly prevented by the GABA_B receptor antagonists, phaclofen and CGP35348, and facilitated by the GABA_B receptor agonist, baclofen, suggesting that GABA_B receptors have an additional inductive role in generation of LTP in the ICC.

The IPSPs examined in the ICC neurons elicited by stimulating the DNLL area or CP close to DNLL have no significant differences in pharmacological properties. These IPSPs are completely blocked by the GABA_A receptor antagonist, picrotoxin, but not affected by the GABA_B receptor antagonist, phaclofen or CGP35348, indicating that the GABAergic inhibition in the ICC is mediated only by postsynaptic

GABA_A receptors. On the other hand, the amplitude of IPSPs is reduced by the GABA_B receptor agonist, baclofen, suggesting that synaptic inhibition is modulated by GABA_B receptors.

The cell membrane input resistance and action potential firing frequency measured in response to depolarizing and hyperpolarizing currents in the DNLL and ICC neurons are reduced significantly by the GABA_A receptor agonist, muscimol, but not affected by the GABA_B receptor agonist, suggesting plenty of GABA_A receptors but relatively few GABA_B receptors on the postsynaptic sites in both DNLL and ICC neurons.

The IPSPs in the DNLL neurons elicited by the CP are completely blocked by the GABA_A receptor antagonist but not affected by both GABA_B receptor antagonists and agonist, suggesting no significant effect of GABA_B receptor on GABAergic inhibition in the DNLL neurons.

The difference in GABA_B receptor action between DNLL and ICC neurons may explain the difference in LTP in these two nuclei. GABA_B receptors in the ICC neurons may serve as autoreceptors to reduce GABA release, suppress GABAergic inhibition, enhance glutaminergic excitation, and thus play an inductive role in development of LTP in the ICC. Lack of GABA_B receptors in the DNLL makes it unlikely to induce typical LTP in the DNLL.

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