Rescue of Inhibitory Synapse Strength following Developmental Hearing Loss

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Abstract

Inhibitory synapse dysfunction may contribute to many developmental brain disorders, including the secondary consequences of sensory deprivation. In fact, developmental hearing loss leads to a profound reduction in the strength of inhibitory postsynaptic currents (IPSCs) in the auditory cortex, and this deficit persists into adulthood. This finding is consistent with the general theory that the emergence of mature synaptic properties requires activity during development. Therefore, we tested the prediction that inhibitory strength can be restored following developmental hearing loss by boosting GABAergic transmission in vivo. Conductive or sensorineural hearing loss was induced surgically in gerbils prior to hearing onset and GABA agonists were then administered for one week. IPSCs were subsequently recorded from pyramidal neurons in a thalamocortical brain slice preparation. Administration of either a GABA A receptor a1 subunit specific agonist (zolpidem), or a selective GABA reuptake inhibitor (SGRI), rescued IPSC amplitude in hearing loss animals. Furthermore, this restoration persisted in adults, long after drug treatment ended. In contrast, a GABA B receptor agonist baclofen did not restore inhibitory strength. IPSCs could also be restored when SGRI administration began 3 weeks after sensory deprivation. Together, these results demonstrate long-lasting restoration of cortical inhibitory strength in the absence of normal experience. This suggests that in vivo GABA A receptor activation is sufficient to promote maturation, and this principle may extend to other developmental disorders associated with diminished inhibitory function.

Introduction

An influential theory in developmental plasticity states that inhibitory synapse function regulates the excitatory synapse critical period [1], [2], [3], [4]. Support for this idea comes from experiments in which the critical period for ocular dominance plasticity (i.e., the reduced cortical activation by a deprived eye) is accelerated or terminated prematurely by agents that augment GABA A receptor-mediated transmission [5], [6], [7]. However, the normal emergence of inhibitory transmission, itself, depends on both spontaneous and driven activity [2], [4], [8]. In the auditory system, developmental deprivation of sound induces a profound reduction of inhibitory strength, and this weakened inhibition persists into adulthood [9], [10], [11], [12], [13], [14]. Here, we evaluate the extent to which cortical inhibitory synapse maturation relies on GABA receptor activation in animals reared with hearing loss.

A reduction in GABA signaling can delay or prevent the maturation of inhibitory synapses. For example, mice lacking the enzyme associated with GABA synthesis, glutamic acid decarboxylase (GAD) 65, do not exhibit ocular dominance plasticity; however, treatment with benzodiazepines restores this mechanism [15]. Similarly, neuronal cultures from mice deficient in GAD67 display a loss of inhibitory terminals on cortical pyramidal cells, but a normal number of anatomical contacts are restored by pharmacological activation of GABAergic transmission [16]. Thus, we reasoned that interventions employing GABAergic agonists immediately following hearing loss could prevent the functional decline of inhibitory strength, even in the absence of normal hearing.

Experimental approaches to repair brain function by modifying inhibition differ depending upon the goal, and the nature of the disorder. For example, research on ocular dominance plasticity seeks to reduce inhibition in adults in order to restore excitatory synaptic plasticity after the critical period has ended [17], [18], [19]. Other investigators have explored stem cell transplantation to facilitate de novo synaptogenesis, and the augmentation of inhibitory drive [20], [21], [22]. Since improved behavioral or neural performance is correlated with stronger GABAergic transmission [23], [24], [25], we sought to reverse the hearing loss-induced dysfunction of inhibitory synaptic strength in the thalamorecipient auditory cortex (ACx).

To test the role of GABA receptor activation, hearing loss was induced prior to hearing onset and GABA agonists were then administered for one week. The amplitude of inhibitory currents was assessed in thalamorecipient ACx neurons in brain slices. Three agents were chosen to activate GABA A receptors only (zolpidem, an a1-subunit potentiator), both GABA A and GABA B receptors (selective GABA reuptake inhibitor, SGRI, 1-[2-[[Di-phenylmethylene]imino]oxy]ethyl]-1,2,5,6-tetrahydroy-3-pyridine-carboxylic acid hydrochloride hydrochloride and GABA B recep-
tors only (baclofen, BAC). Zolpidem and SGRI restored inhibitory strength while BAC treatment was ineffective. Furthermore, inhibitory restoration persisted in adults. These findings suggest that the basic principle of activity-dependent synapse maturation can be used as a strategy to overcome the deficits that may attend early sensory deprivation.

**Methods**

**Animals**

Animal care, maintenance, surgery and pharmacological treatments were in accordance with the guidelines and rules of the Institutional Animal Care and Use Committee, New York University (NYU), approved by the Office of Laboratory Animal Welfare, Office of Extramural Research, and U.S. National Institutes of Health (NIH; Bethesda, MD, USA). See SI Methods for details.

**Hearing loss surgeries**

Gerbil (*Meriones unguiculatus*) pups at postnatal day (P) 10 (P10) were anesthetized with the halogenated ethyl methyl ether methoxyflurane (Metofane). Anesthetic effect occurred by 10 min as tested by an absence of response to nociceptive stimuli (toe pinch). Conductive hearing loss was induced by tympanic membrane puncture and malleus removal. Cochlear ablations were performed on gerbil pups at P10, just prior to the onset of response to airborne sound [10]. See SI Methods for details on sham surgery and sham injection.

**In vivo pharmacological treatment**

A key objective in this study was an attempt to rescue inhibitory synaptic strength following conductive hearing loss. In order to be less invasive and support cortical inhibitory synapses at a slow and sustained level, we subcutaneously administered conductive hearing loss (CHL) pups once everyday for 7 days (i.e. during P11 through P17). We administered the GABA_A receptor α1 subunit-specific agent zolpidem (Sigma, 10 mg/kg), or a selective GABA reuptake inhibitor (SGRI, NO-711 hydrochloride, 1-[2-[[[(Diphenylmethylene)imino]oxy]ethyl]-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid, Sigma, 10 mg/kg), or the GABA_B agonist BAC (Sigma, 2.5 mg/kg). In a separate group of CHL pups, we administered SGRI (10 mg/kg) during P30–36 following CHL.

The doses were determined based on pilot experiments in which zolpidem, SGRI, or BAC was administered in vivo. The initial doses of each drug was 1 mg/kg in 2 CHL animals, and this did not have an apparent effect on spontaneous inhibitory postsynaptic current (sIPSC) amplitudes. The dose was then increased to 10 mg/kg, and this appeared to restore sIPSC amplitude. Therefore, we chose to retain this dose for the study. For BAC, 10 mg/kg led to a decline in motor activity over several days, and we therefore reduced the BAC dosage to 2.5 mg/kg. For a comprehensive outline of the protocol, see Table 1. See SI Methods for details.

**Brain slice preparation and whole cell recordings**

Thalamocortical brain slices (500 µm) were generated as described in our previous papers [10], [11], [12]. See SI Methods for details on whole-cell recordings and selective stimulation of putative unitary afferents for eliciting minimum evoked (m) IPSCs.

**Statistics**

Statistical tests of data distribution were followed by comparisons between groups using commercial software (JMP, SAS).

**Table 1. Experimental groups.**

| Group | P10 | P11–17 | P18–22 | P30–36 | P90–110 |
|-------|-----|--------|--------|--------|---------|
| Control | record | record | record | record | record |
| CHL | record | record | record | record | record |
| CHL | zolpidem | record | record | record | record |
| CHL | SGRI | record | record | record | record |
| CHL | baclofen | record | record | record | record |
| CHL | zolpidem | record | record | record | record |
| CHL | SGRI | record | record | record | record |
| CHL | baclofen | record | record | record | record |
| CHL | zolpidem | record | record | record | record |
| CHL | SGRI | record | record | record | record |
| CHL | baclofen | record | record | record | record |
| Sham surgery | record | record | record | record | record |

**Rescue of inhibitory synaptic currents**

A Shapiro-Wilcoxon W (Goodness-of-fit) test was performed to test for a normal distribution. For those data sets that were not normally distributed, a Wilcoxon rank sums test was performed to determine whether there was a main effect, followed by pairwise comparisons. For the data that were normally distributed, an ANOVA test was performed to determine whether there was a main effect, followed by pairwise comparisons using a Students’ t test.

**Results**

Rescue of inhibitory synaptic strength by GABA_A receptor activation

We first asked whether administration of a GABA_A receptor agonist, zolpidem, could rescue inhibitory synaptic strength in juvenile animals reared with CHL (Fig. 1). As reported previously [14], neurons recorded from juvenile animals with CHL displayed significantly smaller sIPSCs compared to age-matched controls. (mean pA ± SEM; Control: 29.9±3.1, n = 19 (11 animals) vs. CHL: 18.7±2.4, n = 10 (7 animals), χ² = 6.3, p = 0.01; Fig. 1). This finding was reconfirmed by comparing animals with sham surgery to a new group of animals with CHL surgery at P10 (see Suppl. Fig. S1A). When zolpidem was administered for the 7 days immediately following CHL at P10, sIPSCs were significantly larger than those from untreated CHL animals [CHL: 18.7±2.4, institute). A Shapiro-Wilcoxon W (Goodness-of-fit) test was performed to test for a normal distribution. For those data sets that were not normally distributed, a Wilcoxon rank sums test was performed to determine whether there was a main effect, followed by pairwise comparisons. For the data that were normally distributed, an ANOVA test was performed to determine whether there was a main effect, followed by pairwise comparisons using a Students’ t test.
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In the third set of experiments, we asked whether a GABA B receptor agonist did not rescue inhibitory strength. As shown in Figure 3, BAC did not rescue either sIPSC amplitudes when administered to CHL animals for 7 days [mean pA ± SEM: CHL: 18.7±2.4, n = 10 (7 animals) vs. BAC-treated CHL: 15.5±1.8, n = 11 (7 animals), \( \chi^2 = 6.6, p = 0.01 \)]. Furthermore, there was no significant change in either sIPSC amplitude or PPR (Fig. S1).

Rescue of inhibitory synapse strength by a GABA B reuptake inhibitor

We next asked whether administration of a selective GABA B reuptake inhibitor (SGRI) could preserve inhibitory synaptic strength in juvenile animals reared with CHL. As shown in Figure 1, SGRI was also able to rescue sIPSC amplitude when administered to CHL animals for 7 days [mean pA ± SEM: Control: 18.7±2.4, n = 10 (7 animals) vs. SGRI-treated CHL: 34.3±6.5, n = 11 (7 animals), \( \chi^2 = 4.5, p = 0.03 \)]. Furthermore, there was no difference between sIPSCs from control and SGRI-treated CHL animals (Control: 29.9±3.1, n = 19 vs. SGRI-administered CHL: 34.3±6.5, n = 11, \( \chi^2 = 0.005, p = 0.95 \)). SGRI administration in CHL animals also restored me-IPSCs amplitudes [CHL: 5.3±0.5, n = 8 (3 animals) vs. SGRI-treated CHL: 9.4±0.5, n = 7 (3 animals), \( \chi^2 = 10, p = 0.001 \)]. There was no difference between me-IPSCs from control and SGRI-treated CHLs [Control: 12.1±1.3, n = 9 (4 animals) vs. SGRI-treated CHL: 9.4±0.6, n = 7 (3 animals), \( \chi^2 = 2.3, p = 0.1 \)]. In contrast to these results, when animals with sham surgery were treated with SGRI, there was no significant change in either sIPSC amplitude or PPR (Fig. S1).

GABA B receptor agonist did not rescue inhibitory strength

In the third set of experiments, we asked whether a GABA B receptor agonist, could restore inhibitory synapse function in juvenile animals reared with CHL (Fig. 3). Here, we found that BAC did not rescue either sIPSC amplitudes when administered to CHL animals [mean pA ± SEM: CHL: 18.7±2.4, n = 10 (7 animals) vs. BAC-treated CHL: 15.5±1.8, n = 11 (7 animals), \( \chi^2 = 1.1, p = 0.3 \); control: 29.9±3.1, n = 19 (11 animals) vs. BAC-treated CHL: 15.5±1.8, n = 11 (8 animals), \( \chi^2 = 1.02, p = 0.0006 \)]. me-evoked IPSC amplitudes [mean pA ± SEM:
CHL: 5.3±0.5, n = 8 (4 animals) vs. BAC-treated CHL: 7.6±1.8, n = 7 (3 animals), \(\chi^2 = 0.9, p = 0.4\).

Rescue of inhibitory synapse strength persisted in adulthood

CHL induced at P10 leads to a persistent reduction of sIPSC amplitude recorded in adults at P90–110 [14]. Therefore, we asked whether pharmacological reinstatement of inhibitory currents observed in juveniles persisted into adulthood. CHL was induced at P10, and each of the three GABAergic agents was administered to separate groups of CHL animals from P11–17. Animals were weaned at P30, reared until adulthood, and recordings were obtained from brain slices at P90–110.

CHL induced at P10 resulted in a persistent reduction of sIPSC amplitude when recorded in adults at P90–110 (mean IPSC pA ± SEM; Control adult: 27.2±2.7, n = 29 (16 animals) vs. CHL adult: 16.5±2.1, n = 11 (6 animals), \(\chi^2 = 8.2, p = 0.004\) [14]. As shown in Figure 4, the outcome of drug-treatment, when tested in adulthood, was consistent with observations made in juveniles. Administration of either zolpidem or SGRI, but not BAC, preserved sIPSC amplitudes in adult animals reared with CHL (mean pA ± SEM; CHL adult: 16.5±2.1 pA, n = 11 (6 animals) vs. zolpidem-treated CHL adult: 25.6±2.4 pA; n = 9 (6 animals), \(\chi^2 = 5.7, p = 0.01\)). There was no difference between sIPSCs from adult controls and zolpidem-treated CHL adults (Control: 27.2±2.7, n = 29 vs. zolpidem-treated CHL adult: 25.6±2.4; n = 9, \(\chi^2 = 0.3, p = 0.7\)).

The effect of SGRI administration during juvenile development also persisted when sIPSCs were recorded in adult animals [Fig. 4; mean pA ± SEM; CHL adult: 16.5±2.1 pA, n = 11 (7 animals) vs. SGRI-treated CHL adult: 23.6±1.4 pA; n = 6 (4 animals), \(\chi^2 = 3.6, p = 0.05\)]. There was no difference between sIPSCs from adult controls and SGRI-treated CHL adults (Control: 27.2±2.7, n = 29 vs. SGRI-treated CHL adult: 23.6±1.4; n = 6 (4 animals), \(\chi^2 = 0.01, p = 0.89\)). In contrast, BAC-treated CHL animals continued to display IPSCs resembling those of CHL animals when assessed in adulthood (Fig. S3), indicating an absence of restoration (mean pA ± SEM; CHL adult: 18.5±1.2 pA; n = 8 (4 animals), \(\chi^2 = 1.5, p = 0.21\); Control adult: 27.2±2.7, n = 29 vs. BAC-treated CHL adult: 18.5±1.1; n = 8 (4 animals), \(\chi^2 = 3.6, p = 0.05\)).

Rescue of inhibitory strength occurred following bilateral cochlear ablation

To determine whether it is possible to preserve inhibitory strength even after complete loss of auditory afferents, we performed bilateral cochlear ablations at P10, followed by administration of zolpidem from P11–17. Zolpidem rescued sIPSC amplitudes in cochlear-ablated animals, just as it did in CHL animals. Figure 5 shows that neurons recorded from juvenile animals reared with cochlear ablations displayed significantly smaller sIPSCs [mean pA ± SEM; Control: 29.9±3.1, n = 19 (11 animals) vs. ablated: 18.3±1.2 pA; n = 8 (4 animals), \(\chi^2 = 1.5, p = 0.21\); Control adult: 27.2±2.7, n = 29 vs. BAC-treated CHL adult: 18.5±1.1; n = 8 (4 animals), \(\chi^2 = 3.6, p = 0.05\)].
Rescue of inhibitory strength was observed after delayed SGRI administration

To determine whether GABA receptor activation could preserve IPSC strength when treatment was delayed by about 3 weeks from CHL induction, we induced CHL at P10, administered SGRI at P30–36, and raised animals to adulthood. As shown in Figure 6, SGRI could restore sIPSC amplitudes in adults when treatment was delayed [mean ± SEM; adult control: 27.2 ± 2.7, n = 29 (16 animals) vs. SGRI-treated at 30–36 CHL adult: 26.8 ± 3.7; n = 9 (6 animals), χ² = 0.04, p = 0.82; CHL adult: 16.5 ± 2.1, n = 11 vs. SGRI-treated P30–36 CHL adult: 26.8 ± 3.7; n = 9 χ² = 5.75, p = 0.01].

Discussion

Developmental hearing loss may originate in the periphery, yet it causes pervasive impairment of CNS synapses and membrane properties. The disruption of one such property, inhibitory synaptic strength, has been suggested to be a causative factor in many central disorders, including hearing loss [10], [11], [12], [13], [26], [27], [28], [29], [30], [31]. In fact, developmental hearing loss results in weakened inhibitory synaptic strength that persists into adulthood [14]. Our findings suggest that in vivo GABA_A receptor activation is sufficient to promote the maturation of inhibitory synaptic strength in CHL animals, and this principle may apply to other disorders associated with diminished inhibition.

Activity-dependent regulation of developing GABAergic synapses

Converging lines of evidence indicate that inhibitory synapse maturation is facilitated by both spontaneous and driven activity [2], [4], [8]. In the auditory system, disruption of normal activity can perturb both inhibitory synapse strength and the specificity of anatomical projections [32], [33], [34], [35], [36], [37]. Similarly, it has been found that normal activity is necessary for the maturation and maintenance of inhibitory synaptic currents in sensory cortices and dissociated cultures [38], [39], [40], [41], [42], [43], [44], [45]. Consistent with this principle, our results demonstrate that activation of the GABA_A receptor α1 subunit (via zolpidem) or an increase in extracellular GABA at inhibitory synapses (via SGRI action) could each preserve sIPSC amplitude in juvenile animals reared with CHL (Figs. 1, 2). Furthermore, inhibitory strength remained comparable to control levels in adult CHL animals long after drug treatment was terminated (Fig. 4). This finding is broadly consistent with the result that loss of GABA synthesis leads to a reduction of cortical inhibitory boutons and GABAergic transmission, and this can be reversed by activating GABA_A receptors [16], [46].

Temporal window for rescue of inhibitory strength

Descriptive findings from the rodent auditory CNS indicate that many inhibitory synapse properties reach adult-like characteristics within the first 2–3 postnatal weeks [12], [47], [48], [49], [50], [51], [52], [53], [54]. Therefore, we expected that GABAergic activation would no longer rescue inhibitory strength if it were initiated after 4 postnatal weeks. Contrary to this prediction, we found that the time window during which GABA_A receptor activation is sufficient to restore inhibitory strength after CHL extended beyond one month (Fig. 6). Therefore, cortical inhibitory synaptic strength remains sensitive to environmental perturbation after the age when it would normally have reached maturity.

This result is consistent with findings from the visual system suggesting that deprivation extends the critical period. For

Figure 3. Baclofen does not rescue inhibitory strength in juveniles after P10 hearing loss. A Representative sIPSCs recorded in L2/3 pyramidal cells in ACx in slices from animals aged P18 to P22 (V_HOLD = −60 mV). Examples are shown from control (top, black), CHL (middle, orange), and BAC-treated CHL (bottom, olive) animals. B Bar graph (mean ± SEM) of average sIPSC amplitude from all recorded neurons showing diminished sIPSC amplitude in CHL animals is not rescued after treatment with BAC. C Representative traces of minimum-amplitude evoked IPSCs (me-IPSCs) recorded in L2/3 pyramidal cells in ACx in slices from animals aged postnatal day (P) 18 to P22 (V_HOLD = −60 mV). Examples are shown from control (top, black), CHL (middle, orange) and BAC-treated CHL (bottom, olive). In each of these panels, the gray traces represent failures at sub-minimal stimulus intensities. D Bar graph (mean ± SEM) of average me-evoked IPSC amplitude from all recorded neurons showing diminished me-IPSC amplitude in CHL animals is not rescued by treatment with BAC.

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example, when kittens are reared in the dark, it is found that monocular deprivation can continue to induce changes in cortical processing in adult animals [55]. Similarly, in the auditory system, the sensitive period can be extended by rearing animals in a pulsed noise environment [56]. Our results are consistent with a delay in the closure of a sensitive period for inhibitory synaptic maturation. Thus, for animals reared with CHL, we found that late administration of SGRI was able to restore inhibitory strength (Fig. 6). Therefore, our finding indicates that the auditory deprivation due to CHL extended the critical period such that SGRI could induce a positive effect.

Possible mechanism for restoration of inhibitory strength

Injury or inactivation of the cochlea leads to reduced central spontaneous activity during development and into adulthood [57], [58], [59]. Therefore, the enhancement in excitation and...
concomitant decrease in inhibition following severe hearing loss [10] is consistent with a homeostatic response to the decrease in postsynaptic activity [60], [61]. However, if a purely homeostatic mechanism was operative, then GABA_A agonist treatment should not have resulted in more inhibition. Thus, diminished activity does not provide a complete explanation of the outcome. Since these results suggest a non-homeostatic mechanism, it is possible that developing inhibitory synapses display unique responses to manipulations of activity. For example, hearing loss reduces the trafficking of GABA_A subunits into ACx inhibitory synapses [62], and it is possible that GABA_A activation restores this process. Agonist-mediated activation of the inhibitory postsynaptic anchoring protein, gephyrin, can facilitate clustering and restore the GABA_A receptor accumulation [63], [64], [65]. Other GABA_A receptor trafficking mechanisms could operate in synergy with gephyrin to normalize receptor trafficking and restore inhibitory strength [63], [64], [65], [66], [67], [68], [69]. In fact, sustained activation of GABA_A receptors by their potent agonist, muscimol, is also known to facilitate IPSCs via increased trafficking of GABA_A receptors to the postsynaptic membrane [70]. Since the artificial cerebrospinal fluid (ACSF) and internal pipette solution were identical for all groups of animals, it is unlikely that chloride transport mechanisms [71] contribute to our observations.

We have provided evidence that preservation of cortical inhibitory synaptic strength is feasible in animals with moderate or severe hearing loss. Since we do not know the effect of GABA_A agonists on excitatory synapses [72] or voltage-gated channels, it is premature to infer that cortical networks will be fully restored following the pharmacological procedures employed here. However, the impact of GABAergic activation does persist long after treatment ceases [Figs. 4, and 6], suggesting that the potential ameliorative effect of pharmacological treatment can be tested behaviorally [73].

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