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PHARMACOLOGICAL AND DEPRIVATION-INDUCED REINSTATEMENT OF JUVENILE-LIKE LONG-TERM POTENTIATION IN THE PRIMARY AUDITORY CORTEX OF ADULT RATS

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Abstract—Sensory cortices show a decline in synaptic plasticity (e.g., long-term potentiation, LTP) during postnatal maturation. We demonstrate a partial reversal of this decline in rat primary auditory cortex (A1) by pharmacological manipulations or modifications of the acoustic environment. In adult, anesthetized rats, field postsynaptic potentials (fPSPs) in A1 elicited by medial geniculate nucleus (MGN) stimulation consisted of two sequential peaks. Simultaneous application in A1 of a $GABA_A$ receptor agonist (muscimol) and $GABA_B$ receptor antagonist (SCH 50911), thought to result in a preferential inhibition of intracortical activity while preserving thalamocortical inputs, suggested that these two fPSP components largely reflect thalamocortical and intracortical synapses, respectively. Rats (postnatal day [PD]60–70) showed moderate LTP of fPSPs following theta-burst stimulation (TBS) of the MGN. Interestingly, repeated episodes (PD10–20 & 50–60) of patterned sound deprivation by continuous white noise exposure resulted in substantial LTP, an effect not seen with single exposure (PD10–20 or 50–60), or two episodes during adulthood (PD50–60 & 100–110). Thus, early sensory deprivation acts as a "prime," allowing subsequent deprivation to reinstate juvenile-like levels of LTP. Older (>PD200) rats that no longer exhibit LTP in A1 showed LTP of the first fPSP peak when TBS occurred during cortical zinc application. We conclude that the age-related decline of plasticity in A1 can be partially reversed by pharmacological techniques or manipulations of the acoustic environment during specific periods of postnatal life.

Key words: audition, sensory deprivation, white noise exposure, NMDA receptor, zinc.

Sensory experience plays an important role in regulating levels of cortical plasticity throughout the lifespan of an animal. Developmentally regulated and sensory-dependent modifications of N-methyl-D-aspartate (NMDA) receptor (NMDAR) subunit composition can influence the ability of synapses to undergo plastic change (Bear, 2003; Kopp et al., 2007). In primary visual (V1) and auditory cortices (A1), levels of NR2B subunits of the NMDAR are high at birth and remain high, whereas levels of NR2A subunits are initially low and increase with age and concomitant sensory experience (V1: Quinlan et al., 1999; Philpot et al., 2001; Chen and Bear, 2007; A1: Hsieh et al., 2002; Bi et al., 2006). Given that excitatory postsynaptic currents of NR2B-containing NMDARs permit enhanced Ca^{2+} entry into postsynaptic cells, greater relative NR2B subunit levels are thought to facilitate plasticity (Monyer et al., 1994; Flint et al., 1997), which may act as one of several mechanisms underlying enhanced critical period plasticity (Bear, 2003). It is noteworthy, however, that the configuration of NMDAR subunits is only one of multiple factors influencing critical period plasticity. For example, it is well recognized that maturation of the intracortical GABAergic system acts as another important regulator of critical period onset and duration (Hensch, 2004; Jiang et al., 2005).

Given the enhanced plasticity apparent during critical periods and in immature cortical circuits, it is not surprising that induction thresholds for long-term potentiation (LTP) in various sensory cortices are significantly lower in young animals (Kato et al., 1991). For example, in A1, juvenile (30–35 day old) rats show the greatest levels of LTP, which declines into adulthood and can no longer be elicited in rats >200 days of age (Hogsden and Dringenberg, 2009a). Notably, the LTP enhancement in juvenile rats is greatly reduced with application of an NR2B antagonist (Ro 25-6981), highlighting the role of this subunit in the expression of greater levels of plasticity in young animals (Hogsden and Dringenberg, 2009a).

Sensory deprivation during early postnatal life disrupts the typical, developmental alteration in NMDAR subunit composition. In rodents, visual deprivation by means of dark-rearing attenuates the developmental increase in NR2A subunits, resulting in the maintenance of a low NR2A:NR2B ratio, which is thought to extend the critical period for ocular dominance plasticity in V1 (Quinlan et al., 1999). Similarly, masking patterned sound during early postnatal life via continuous white noise (WN) exposure arrests the development of highly organized, adult-like tonotopicity in the rodent A1 and leads to the persistence of heightened, juvenile-like LTP into adulthood (Chang and Merzenich, 2003; Speechley et al., 2007; Hogsden and Dringenberg, 2009b). Consequently, continuous white noise exposure can be considered a form of sensory de-

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Abbreviations: aCSF, artificial cerebral spinal fluid; ANOVA, analyses of variance; AP, anteroposterior; A1, primary auditory cortex; Ca^{2+}, calcium; dB, decibel; fPSP, field postsynaptic potential; L, lateral; LTP, long-term potentiation; MGN, medial geniculate nucleus; NMDA, N-methyl-D-aspartate; PD, postnatal day; SEM, standard error of the mean; SPL, sound pressure level; TBS, theta-burst stimulation; V, ventral; V1, primary visual cortex; WN, white noise; Zn^{2+}, zinc ions.

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privation, as it masks patterned acoustic inputs necessary for cortical development. Notably, white noise-induced LTP enhancements can be reversed with application of NR2B antagonists in A1 (Hogsden and Dringenberg, 2009b), consistent with a role of sensory experience in regulating the levels of NMDAR subunits and plasticity in maturing sensory cortices. Together, these data are consistent with the notion that the ratio of NR2A:NR2B subunits is an important regulator of plasticity levels during postnatal life, with greater relative levels of NR2B promoting plasticity, while increasing levels of NR2A result in resistance to synaptic reorganization (Quinlan et al., 1999; Bear, 2003).

Despite the fact that plasticity induction is hindered by the developmental processes described above, significant levels of plasticity can be expressed in fully matured sensory cortices (e.g., Weinberger, 2004, 2007; Hofer et al., 2006a). Importantly, the susceptibility to synaptic modifications can be influenced by previous episodes of experience-dependent synaptic reorganization. Hofer et al. (2006b) demonstrated that a monocular deprivation regimen, found to be ineffective when applied only once to adult mice, resulted in an ocular dominance shift in the mature V1 when repeated episodes were administered over time. Remarkably, this effect was observed regardless of whether the first deprivation episode occurred during the critical period for ocular dominance plasticity or in adulthood (Hofer et al., 2006b). Similarly, re-alignment between spatial auditory and visual maps in the optic tectum of adult barn owls (induced by exposure to prism goggles that shifted the visual field) occurred more readily when owls had prior experience wearing the goggles as juveniles (Knudsen, 1998). These findings are significant since they suggest that plasticity events at an earlier time can prime neurons for the expression of subsequent, synaptic rearrangements.

Given the findings reviewed above, we asked whether repeated episodes of patterned sound deprivation with white noise exposure can enhance and restore juvenile-like levels of LTP in A1. We also explored whether the first episode of white noise exposure must occur during the critical period for auditory development (de Villers-Sidani et al., 2007), and if there are temporal limits between repeated exposure periods for plasticity facilitation to occur. In addition, we also examined the effect of intracortical zinc ($ZnCl_2$) application, known to act as an antagonist of NR2A subunits, on LTP in older (>200 days old) rats. This range was chosen since rats at this age typically no longer show LTP in A1, and fall outside the temporal limits that appear to govern plasticity facilitation by prior sensory deprivation. We hypothesize that zinc application will restore LTP in these rats, possibly by means of lowering the NR2A:NR2B ratio.

EXPERIMENTAL PROCEDURES

Animals

All subjects were obtained from Charles River (St. Constant, Quebec) and treated in accordance with the regulations on animal experimentation established by the Canadian Council on Animal Care. All experimental procedures were approved by the Queen's University Animal Care Committee.

Male Long-Evans rats were obtained (45–50 days old) and housed four per cage in a colony room under unaltered acoustic conditions until they reached the appropriate age for testing. The colony room was maintained on a 12–12 h reverse light cycle, lights on at 1900 h, with food and water available *ad libitum*.

For experimental groups that received white noise exposure during early postnatal life (from postnatal day [PD]10–20), untimed (~19 days) pregnant female Long-Evans rats were obtained. In a separate colony room, these pregnant rats were singly-housed in cages upon arrival (food and water available *ad libitum*). Cages were situated in a sound-attenuated chamber ($114\times61\times66$ cm^3, plywood lined with aluminium, fitted with a time controlled light, fan, and two equally spaced speaker boxes mounted on the ceiling of the box). Following birth, offspring were housed with their mothers until weaning (PD21), at which point the mothers and female offspring were removed from the cages, and males were separated into cages containing no more than four rats.

White noise exposure

Within the sound attenuated chamber, each of the two ceiling-mounted speaker boxes contained two speakers (one 8 inch woofer and one 3.25 inch tweeter, frequency ranges of 45 Hz–5 kHz and 2 kHz–35 kHz, respectively, American Legacy Series 2 Speakers, Legacy Audio, Brooklyn, NY, USA). The speakers were connected to a custom-made white noise generator (Department of Psychology, Electronics Workshop, Queen's University). Previous spectral analyses of the sound signal recorded inside the chamber showed that white noise generated with this apparatus covers a frequency range up to ~35 kHz, with power gradually declining between 30 and 37.5 kHz (Speechley et al., 2007). Even though rats are sensitive to sounds at frequencies above 35 kHz, previous mapping studies have demonstrated that the large majority of neurons in A1 are optimally responsive to frequencies within the range generated by this apparatus (Kilgard and Merzenich, 1999; Chang and Merzenich, 2003). Sound attenuation across the chamber wall is ~27 dB sound pressure level (SPL) for a white noise signal of ~80 dB SPL generated inside the chamber (Hogsden and Dringenberg, 2009b).

For rats reared on the premises, continuous white noise exposure began at PD5, which is approximately 5–6 days prior to the onset of low-threshold hearing in the rat (de Villers-Sidani et al., 2007). Over a five day-period, white noise sound volume was increased incrementally from ~65 to ~80 dB SPL to minimize stress experienced by the mother. Subsequently, white noise was maintained at this level from PD10 to 20, at which point all rats were removed from the chamber and placed in a regular colony room under unaltered sound conditions. Some of these rats received a second white noise exposure from either PD50 to 60–70 or PD100 to 110–120. Electrophysiological procedures were carried out in these groups between PD60–70 or PD110–120. In all cases where rats were exposed to white noise during adulthood (also see below), a three day-acclimatization period was given (e.g., PD47 to 50) during which rats were housed in the sound attenuated chamber and white noise levels increased gradually from ~65 to ~80 dB SPL.

An additional group of rats was placed in the white noise chamber only during adulthood (PD50 to 60–70) and tested at PD60–70. Finally, one group of rats received repeated episodes of white noise exposure during adulthood (PD50 to 60 and PD100 to 110–120, tested at PD110–120). Between these two exposure periods, rats were returned to the unaltered sound environment.