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Toluene exposure during brain growth spurt and adolescence produces differential effects on N-methyl-D-aspartate receptor-mediated currents in rat hippocampus

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ABSTRACT

Toluene, an industrial organic solvent, is voluntarily inhaled as drug of abuse. Because inhibition of N-methyl-D-aspartate (NMDA) receptors is one of the possible mechanisms underlying developmental neurotoxicity of toluene, the purpose of the present study was to examine the effects of toluene exposure during two major neurodevelopmental stages, brain growth spurt and adolescence, on NMDA receptor-mediated current. Rats were administered with toluene (500 mg/kg, i.p.) or corn oil daily over postnatal days (PN) 4–9 (brain growth spurt) or PN 21–26 (early adolescence). Intracellular electrophysiological recordings employing in CA1 pyramidal neurons in the hippocampal slices were performed during PN 30–38. Toluene exposure during brain growth spurt enhanced NMDA receptor-mediated excitatory postsynaptic currents (EPSCs) by electrical stimulation, but impaired the paired-pulse facilitation and NMDA response by exogenous application of NMDA. Toluene exposure during adolescence resulted in an increase in NMDA receptor-mediated EPSCs and a decrease in exogenous NMDA-induced currents, while lack of any effect on paired-pulse facilitation. These findings suggest that toluene exposure during brain growth spurt and adolescence might result in an increase in synaptic NMDA receptor responsiveness and a decrease in extrasynaptic NMDA receptor responsiveness, while only toluene exposure during brain growth spurt can produce presynaptic modulation in CA1 pyramidal neurons. The functional changes in NMDA receptor-mediated transmission underlying developmental toluene exposure may lead to the neurobehavioral disturbances.

1. Introduction

The chronic abuse of volatile solvents is a growing problem among children and adolescents at social risk worldwide. Toluene is one of the most commonly abused solvents. Since a large number of abusers are adolescent and young adult women in their childbearing years, there are raising concerns about the potential negative impact of intentionally inhaled organic solvents on the unborns.

Abuse of toluene by pregnant women can lead to an embryopathy, also referred to as the fetal solvent syndrome. Characteristics of toluene embryopathy include particular craniofacial features, growth retardation, and central nervous system dysfunctions such as microcephaly, brain malformation, and motor and intellectual disability (Pearson et al., 1994). Nevertheless, not all offspring of mothers exposed to toluene show evident physical features and structural damage. Those who exposed to lower doses or shorter duration of toluene might still have important but subtle impairment in synaptic circuitry, reflecting as neurobehavioral disturbance. However, neuron developmental evaluations of these children have not been reported.

The N-methyl-D-aspartate (NMDA) receptor plays an important role in neurodevelopment, neuroplasticity, neuroendocrine regulation, and neuronal death (Contestabile, 2000; Cull-Candy et al., 2001; Scheetz and Constantine-Paton, 1994). Experimental evidence indicates that the effects of toluene on neuronal activity and behavior might be due to its inhibition of NMDA receptor-mediated currents (Cruz et al., 1998). Our previous studies demonstrated that exposure to toluene during brain growth spurt enhances the NMDA-induced seizure susceptibility (Chen and Lee, 2002), increases the immunoreactivity of NR2A subunit in the hippocampus and cerebellum (Lee et al., 2005), and reduces NMDA antagonist-induced locomotor activity, motor incoordination and hypnosis (Chien et al., 2005) in juveniles. We also demonstrated that neonatal toluene exposure dose-dependently reduced intracellular Ca^{2+} signals in response to glutamate/glycine and NMDA/glycine in cultured cerebellar granule neuron (Chen et al., 2005). Therefore, it is possible that dysregulation of NMDA

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receptor-mediated transmission may play an important role in the pathophysiology of toluene-related neurodevelopmental disorders.

The period of brain growth spurt that largely occurs during the third trimester of human fetal development but occurs during the early postnatal period in the rats (Dobbing and Sands, 1979), is a dynamic period of central nervous system (CNS) development that has been shown to be particularly vulnerable to a variety of neurotoxicants. On the other hand, adolescence is also a time of extensive pruning of synapses and of reorganization of many neurotransmitter systems (Spear, 2000). Temporary interference with the function of neurons with NMDA receptors by toluene exposure during brain growth spurt or adolescence is likely to disturb the normal development of CNS, subsequently resulting in long-lasting functional changes in NMDA receptors. The purpose of this study was to test the effects of toluene exposure during brain growth spurt or early adolescence on NMDA receptor-mediated excitatory response. To differentiate the influence of toluene on the synaptic and extrasynaptic NMDA receptor-mediated currents, electrical stimulation and exogenous application of NMDA were used to evoke excitatory postsynaptic currents (EPSCs). In addition, a paired-pulse paradigm was employed to reveal the involvement of presynaptic mechanism.

2. Materials and methods

2.1. Materials

Toluene (HPLC grade, 99.8%) was obtained from Mallinckrodt Baker (Phillipsburg, NJ, USA). Glycine was purchased from J.T. Baker (Mallinckrodt Baker, Inc., Kentucky, USA). All other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

2.2. Animal treatment

Pregnant female Sprague-Dawley rats were supplied from the Laboratory Animal Center of Tzu Chi University (Hualien, Taiwan). Rats were housed individually on a 12/12 light-dark cycle at 22 °C. All experiments were performed in accordance with the Republic of China animal protection law (Chapter III: Scientific Application of Animals) and approved by Review Committee of the Tzu Chi University.

2.3. Toluene exposure

The day of birth was considered to be postnatal day (PN) 0. The litters were culled to 10–12 pups and each litter was randomly assigned to toluene or control group. Male animals received 500 mg/kg of toluene (0.1 g/ml in corn oil) or corn oil (0.1 ml/10 g) by intraperitoneal injection daily over brain growth spurt (PN 4–9) or adolescence (PN 21–26). A modified 26 G needle (6 mm long) was used for the pups to prevent tissue damage. The mother did not reject the pups treated with toluene. All the pups were weaned on PN 21.

In general, human exposed to toluene by inhalation. Continuous exposure to toluene vapors is usually used in rodent models to mimic the exposure in industrial workers. However, abusers do not continuously sniff glue for long period, but rather prefer to titer their dose by repeatedly 'huffing' very-high-exposure concentrations for only seconds to minutes. This is hard to be conducted in animal models. Actually, intraperitoneal injection of toluene to rodents, like inhalation exposure, produced biphasic locomotor activity and stereotypic behaviors, which resemble behavioral signs observed in toluene abusers (Chan et al., 2004; Riegel and French, 1999) and full substitution for inhaled toluene in drug discrimination (Shelton and Slavova-Hernandez, 2009). The concentration of toluene in the animal tissues at the time of testing determined the behavioral performance no matter the route of administration (Shelton and Slavova-Hernandez, 2009). Furthermore, intraperitoneal injection can produce low variation of toluene concentrations in blood and this route of administration is also routinely used in animals to study drugs commonly abused by inhalation (e.g., cannabinoids and nicotine). Therefore, toluene was administered by intraperitoneal injection.

The toluene dose (500 mg/kg) used in this study was based on our previous studies. Rats subjected to a similar toluene exposure dose and paradigm (PN 4–9) manifested increasing NMDA-induced seizure susceptibility, reducing behavioral responses to NMDA antagonists, and blood toluene concentrations, from blood sample taken 1 and 3 h following the last injection of toluene, were 27.4 ± 5.1 μg/ml and 7.8 ± 1.5 μg/ml, respectively (Chien et al., 2005; Lee et al., 2005). These levels are in the range obtained from toluene abusers (0.1–74.7 μg/ml) (Garriott et al., 1981; Park et al., 1998; Zanatta et al., 1996). In addition, the placenta penetration efficiency for toluene is greater than 90% (Shumilina, 1991).

2.4. In vitro electrophysiology, stimulation, and drug application

Experiments were performed on hippocampal slices obtained from control or toluene-exposed rats at PN 30–38. The brain was quickly removed from the skull and placed in an ice-cold artificial cerebrospinal fluid (ACSF) containing (in mM): NaCl 120, KCl 3.5, $MgCl_2$ 1.2, $CaCl_2$ 2.5, NaH_2PO_4 1.2, glucose 11.5, $NaHCO_3$ 25, saturated with 95% O_2 and 5% CO_2, pH 7.4. Transverse hippocampal slices (500 μm) were cut with a vibratome and stored at room temperature in holding the same ACSF solution as above. After a recovery period of at least 1 h, an individual slice was transferred to the recording chamber where it was continuously superfused with oxygenated ACSF at a rate of 2–3 ml/min. CA1 pyramidal neurons were voltage clamped at −60 mV to record NMDA receptor-mediated EPSCs. Patch pipettes were filled with a solution containing (in mM): K gluconate 122, NaCl 5, $CaCl_2$ 0.3; $MgCl_2$ 2, EGTA 1, HEPES 1, Na_2ATP 5, NaGTP 2, amphotericin B 0.4 (pH 7.25, resistance 9–12 M). Orthodromic stimuli were delivered with square-wave pulses (5–16 V; 0.1 ms) via a concentric bipolar electrode which was placed in stratum radiatum to activate Schaffer collaterals. Current signals and applied voltages were generated and recorded with an Axoclamp 200B amplifier (Axon Instruments, USA). Whole-cell recording are acquired with a switch frequency of 5–6 kHz (30% duty cycle), gain of 3–8 nA/mV, time constant 20 ms. Tracings shown in figures represent the average of three consecutive sweep. Output signals were stored on an IBM-compatible computer after digitalization with a DigiData-1200 Series Interface using acquisition and analysis software (pClamp, v. 8.10). In order to isolate NMDA receptor-mediated monosynaptic EPSCs, the AMPA/kainate receptor antagonist DNQX (50 μM), γ-aminobutyric acid A ($GABA_A$) receptor antagonists bicuculline (10 μM) and picrotoxin (10 μM), and $GABA_B$ receptor antagonist CGP35348 (200 μM) were applied together as a cocktail. NMDA (10, 20 and 50 μM) and glycine (10 μM) applied by bath superfusion to achieve steady-state concentrations within the 1.0-ml recording chamber.

For paired-pulse facilitation, two stimuli (15 V) were delivered with an interstimulus interval of 40–200 ms. The facilitation was calculated as the current ratio ($EPSC_2$//$EPSC_1$).

2.5. Statistics

All values were given as mean ± SEM. Two-way mixed designed ANOVA was used for the stimulus-induced NMDA current and paired-pulse facilitation. Two-way ANOVA was used for exogenous NMDA-elicited currents. Multiple comparisons were performed using the Student–Newman–Keuls test. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Body weight gain

During the time of toluene exposure (PN 4–9 or PN 21–26), the body weight gain of the toluene-exposed (12.5 ± 1.2 g; 28.8 ± 1.7 g) and control rats (12.3 ± 1.3 g; 27.6 ± 2.0 g) was similar.

3.2. Effects of toluene exposure on NMDA receptor-mediated EPSCs

The effect of toluene exposure during brain growth spurt on NMDA receptor-mediated EPSCs was examined by voltage clamp recordings after appropriate pharmacological isolation to block the AMPA/kainate receptor-mediated components of the EPSCs and GABA-mediated components of the inhibitory postsynaptic currents (IPSCs). The composite EPSCs provoked by electrical stimulation were blocked by the NMDA receptor inhibitor D(−)-2-amino-5-phosphonopentanoic acid (D-APV, 50 μM) (Fig. 1B). Two-way mixed designed ANOVA revealed a main effect of treatment ($F_{1,216} = 22.68$, $p < 0.001$) and stimulus intensity ($F_{8,216} = 67.24$, $p < 0.001$) with significant interaction ($F_{8,189} = 8.19$, $p < 0.001$). *Post hoc* analysis indicated EPSCs in response to 8–16 V stimuli were significantly elevated in the slice from toluene-exposed rats (Fig. 1A and B).

In the adolescent exposure study, the NMDA receptor-mediated EPSCs were significantly increased (*Treatment*: $F_{1,198} = 4.47$, $p = 0.045$; *Stimulus intensity*: $F_{8,198} = 56.82$, $p < 0.001$; *Interaction:* $F_{8,198} = 2.87$, $p = 0.042$) by toluene exposure. *Post hoc* analysis showed that the currents in response to 12–16 V stimuli were significantly higher in the slice from toluene-exposed rats than controls (Fig. 1C).

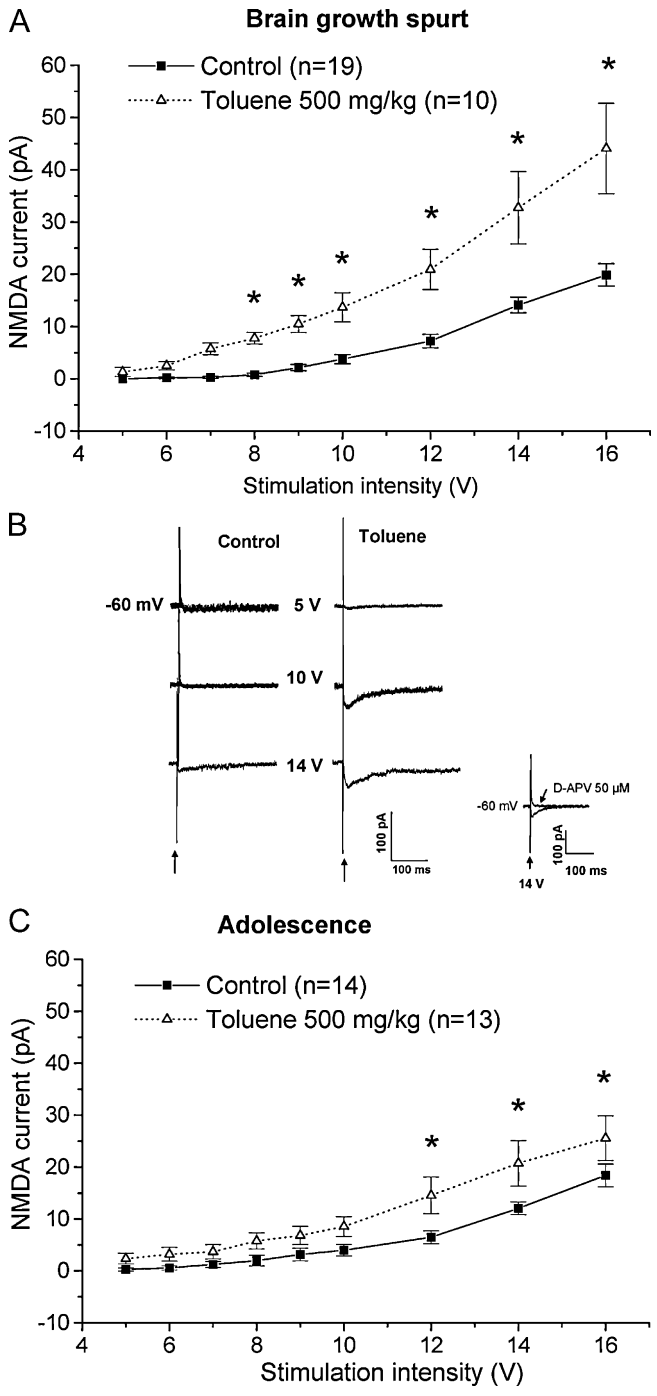

Fig. 1. Effects of toluene exposure on NMDA receptor-mediated EPSCs evoked by Schaffer collateral stimulation of CA1 pyramidal neurons in the hippocampal slices. The input–output relationship of EPSCs depicted following toluene exposure during brain growth spurt (A) and adolescence (C). Representative traces illustrating synaptic NMDA receptor currents recorded (V_H = −60 mV) in neurons from controls and rats exposed to toluene during brain growth spurt (B). Data are mean ± SEM. *$p < 0.05$ compared with control groups.

3.3. Effects of toluene exposure on NMDA currents evoked by exogenous application of NMDA

When the hippocampal slice preparations were superfused with 10 μM, 20 μM, or 50 μM of exogenous NMDA after pharmacological isolation, the NMDA currents recorded from the neurons of rats exposed to toluene during brain growth spurt period were significantly lower than controls (*Treatment*: $F_{1,52} = 50.28$, $p < 0.001$, *NMDA concentration*: $F_{2,52} = 32.01$, $p < 0.001$, *Interaction*: $F_{2,52} = 0.04$, $p = 0.955$). *Post hoc* analysis indicated toluene exposure significantly decreased the currents in responses to NMDA at concentrations of 10, 20, and 50 μM (Fig. 2A). The NMDA currents of the hippocampal slice from the rats exposed to toluene during adolescence were also reduced (*Treatment*: $F_{1,31} = 4.76$, $p = 0.037$; *NMDA concentration*: $F_{2,31} = 6.859$, $p < 0.01$; *Interaction*: $F_{2,31} = 0.363$, $p = 0.699$) *Post hoc* analysis indicated toluene exposure significantly decreased the currents in responses to NMDA at concentrations of 10 and 50 μM (Fig. 2B).

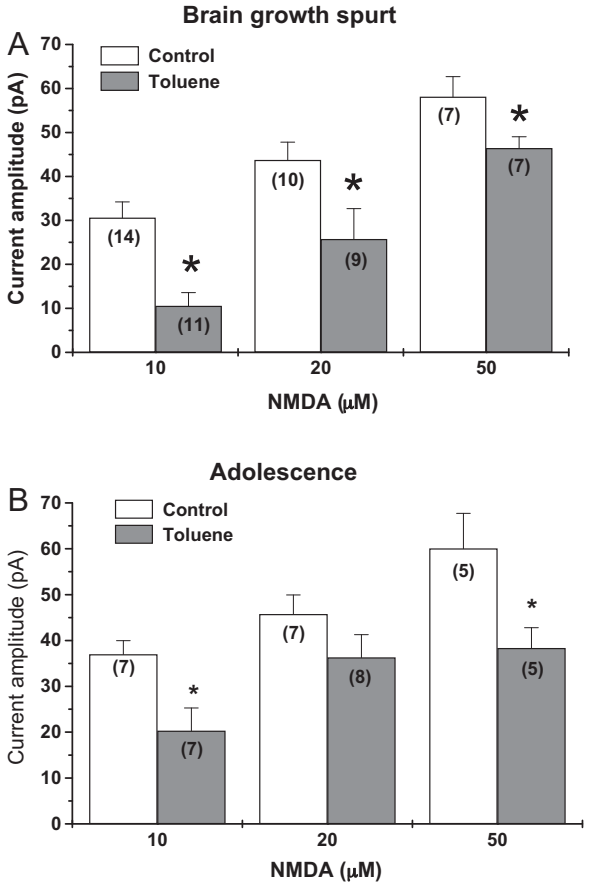

Fig. 2. Effects of toluene exposure on NMDA receptor-mediated EPSCs by exogenous application of NMDA. Amplitudes in response to NMDA (10–50 μM) perfusion recorded at holding potential of −60 mV in the hippocampal CA1 pyramidal neurons in controls, rats exposed to toluene during brain growth spurt (A) and adolescence (B). Data are mean ± SEM. *$p < 0.05$ compared with control groups.

3.4. Effects of toluene exposure on NMDA–EPSC pairs

The amplitude of the second of a pair of composite NMDA–EPSCs is greater relative to that of the first pulse and the magnitude of this increase is dependent on the stimulus interval between the EPSCs in control rats. Stimulus intervals of 40–100 ms showed markedly paired-pulse facilitation, whereas this enhanced effect disappeared at intervals of 120–200 ms (Fig. 3). Two-way mixed designed ANOVA revealed that toluene exposure during brain growth spurt period significantly decreased the paired-pulse facilitation at 40–100 ms stimulus interval (*Treatment*: $F_{1,96} = 10.95$, $p < 0.01$; *interval*: $F_{8,96} = 5.032$, $p < 0.001$; *Treatment* × *Interval*; $F_{8,96} = 2.629$, $p = 0.012$) (Fig. 3B). However, there was no significant difference between the controls and adolescent toluene-exposed rats (*Treatment*: $F_{1,80} = 0.555$, $p = 0.473$; *Interval*: $F_{8,80} = 10.388$, $P < 0.001$; *Treatment* × *Interval*: $F_{8,96} = 1.346$, $p = 0.233$) (Fig. 3C).

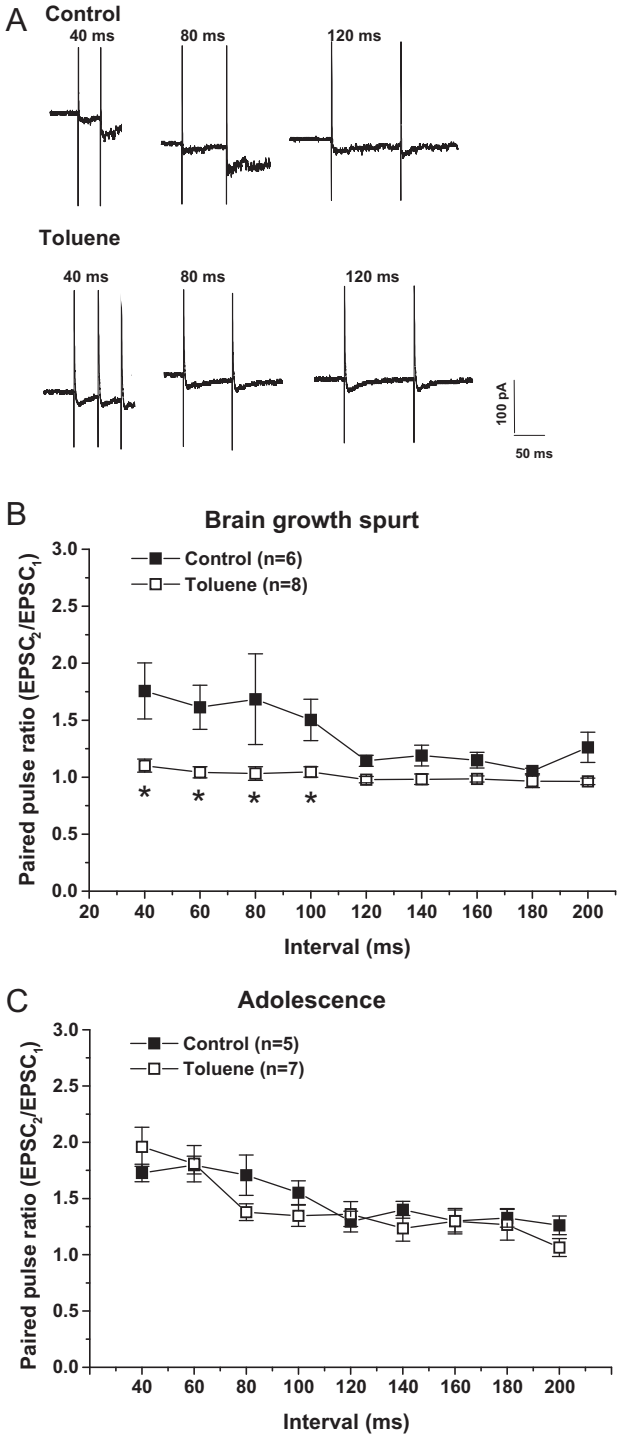

Fig. 3. Effect of toluene exposure on paired-pulse facilitation of the NMDA EPSCs. NMDA–EPSCs were recorded at −60 mV from CA1 pyramidal neurons in hippocampal slices at stimulus intervals ranging from 40 to 200 ms. Stimulus intensity used was 15 V. Representative traces illustrating the degree of paired-pulse facilitation (A). The paired pulse ratios of NMDA–EPSCs amplitudes recorded at 40–200 ms stimulus intervals in controls, rats exposed to toluene during brain growth spurt (B) and adolescence (C). Data are mean ± SEM. $^*p < 0.05$ compared with control groups.

4. Discussion

Toluene exposure during brain growth spurt enhanced NMDA receptor-mediated EPSCs by electrical stimulation, yet reduced paired-pulse facilitation and NMDA response by exogenous application of NMDA. Toluene exposure during adolescence also resulted in an increase in NMDA receptor-mediated EPSCs and a decrease in exogenous NMDA-induced response, while lacking any effect on paired-pulse facilitation. These results show that the effects of developmental toluene exposure on NMDA receptor-mediated transmission in hippocampal CA1 neurons are similar, although brain growth spurt period seems more sensitive than adolescence to toluene exposure. As paired-pulse facilitation in the hippocampus is primarily mediated by an enhancement of presynaptic glutamate release, the distinct effects of toluene exposure during these two developmental stages on paired-pulse facilitation suggest the presynaptic glutamate release is altered by toluene in an age-dependent manner. Even though it has been reported that blood toluene concentrations are unaffected by age (Gordon et al., 2010), brain pharmacokinetic differences between pups and adolescent rats might be one of the contributing factors to their different susceptibility.

Orthodromic stimulation activates predominately synaptic receptors, whereas exogenous application of NMDA would be expected to activate primarily extrasynaptic receptors and to a lesser extent synaptic receptors. The disparate effects of toluene exposure during brain growth spurt on NMDA receptor-mediated EPSCs and tonic NMDA currents could be obtained since the synaptic and extrasynaptic NMDA receptors might have distinct compositions. NMDA receptors are composed of two NR1 subunits with one or more NR2A, NR2B, NR2C, NR2D, or NR3 subunits, and differences in neuronal NMDA receptor properties are largely attributed to the NR2 subunits (Cull-Candy and Leszkiewicz, 2004). NR2B are strongly expressed early in development, and NR2A expression increases during development (Monyer et al., 1994). The subunit composition of extra-synaptic and synaptic NMDA receptors in mature hippocampal neurons is asymmetrical. Synaptic NMDA receptors contain NR2A (predominantly) and NR2B subunits, whereas extrasynaptic NMDA receptors contain mostly NR2B subunits (Tovar and Westbrook, 1999) and NR2D subunits (Thompson et al., 2002). The present data showed that NMDA receptor-mediated EPSCs by electrical stimulation are elevated after toluene exposure during brain growth spurt and adolescence, indicating the enhancement of the synaptic NMDA receptor function. In parallel, our previous studies demonstrated that toluene exposure during brain growth spurt increases the immunoreactivity of NR2A subunit in the hippocampus (Lee et al., 2005). Because NR2A-containing receptors are mainly located synaptically, increased levels of NR2A subunits may contribute to the synaptic NMDA receptor functional changes after toluene exposure during brain growth spurt. It remains to be investigated whether toluene exposure during adolescence can also enhance NR2A subunit expression.

The exogenous NMDA-induced responses were remarkably reduced by toluene exposure during brain growth spurt and adolescence. Although bath application of NMDA presumably activates both synaptic and extrasynaptic NMDA receptors, the functional alterations in extrasynaptic NMDA receptors might mainly contribute to the reduced responses because the EPSCs were increased rather than decreased by toluene exposure. Our previous study has shown that toluene exposure during brain growth spurt dose-dependently reduces intracellular Ca^{2+} signals in response to glutamate/glycine and NMDA/glycine in cultured cerebellar granule neuron (Chen et al., 2005), which is attributed to the decreased NR2B subunit expression. Based on the predominance of NR2B subunit in NMDA extrasynaptic receptors, the specific reduction of extrasynaptic NR2B-containing NMDA receptors might be also related to the lower response to NMDA-induced current after toluene exposure.

Our previous studies revealed that toluene exposure during brain growth spurt enhances NMDA-induced seizure suscepti-

bility (Chen and Lee, 2002), which might be associated with the reduction of the tonic NMDA receptor currents (primarily mediated by extrasynaptic receptors). It has been shown that electrographic seizures in organotypic hippocampal slice cultures were dramatically increased and the amplitude of tonic NMDA receptor-mediated currents was reduced following chronic treatment with the high-affinity competitive antagonist, D(−)-2-amino-5-phosphonopentanoic acid (D-APV) (Bausch et al., 2010). Like D-APV, toluene inhibits NMDA receptor currents. Our data showing tonic NMDA receptor currents were significantly reduced following toluene exposure during brain growth spurt, further support the early observations of the inverse relationship between changes in extrasynaptic NMDA receptor function and alterations in seizure expression following subchronic NMDA receptor inhibition.

In addition to increasing the synaptic NMDA receptor-mediated current, toluene exposure during brain growth spurt significantly decreased paired-pulse ratio of these EPSCs. Paired-pulse facilitation is a phenomenon of short-term plasticity whereby a second synaptic response is enhanced by a preceding stimulation of similar intensity. Our data demonstrate that in response to a pair of stimuli with stimulus interval between 40 and 100 ms, the response to a second stimulus was significantly facilitated in control animals, but not in the rats exposed to toluene during brain growth spurt. The paired-pulse facilitation in the hippocampus depends on the release probability of glutamate, a presynaptically mediated phenomenon (Bonci and Williams, 1997; Dobrunz and Stevens, 1999; Mennerick and Zorumski, 1995; Zucker and Regehr, 2002), and on the post-synaptic effect of ligands of the receptor (Wang and Kelly, 1997). It is likely that the attenuation of paired-pulse facilitation by toluene exposure during brain growth spurt may be, at least in part, associated with the high initial probability of presynaptic glutamate release in hippocampal CA1 neurons, i.e., the release caused by the first stimulus in a pair is closer to its maximal value, leaving less room for further facilitation of the glutamate release. When a paired-pulse procedure was employed with NMDA–EPSCs in hippocampal CA1 neurons from adolescent toluene-exposed rat, there was no difference in the ratios of the first and second responses obtained from toluene as compared with control rats. These data suggested that adolescent toluene exposure might not affect presynaptic glutamate release.

In summary, the present data demonstrated that toluene exposure during brain growth spurt enhances NMDA receptor-mediated EPSCs and presynatic glutamate release, but reduces the extrasynaptic NMDA receptor function in the hippocampal CA1 pyramidal neurons. Adolescent toluene exposure produces similar effects on NMDA receptor-mediated synaptic responses and extrasynaptic NMDA receptor activity, but does not influence on presynaptic glutamate release. Our findings support the developmental risk of toluene exposure and suggest that long-lasting NMDA receptor dysfunction might play a role in the developmental impairment and neurobehavioral aberrations displaying in children born to mothers who abused toluene and might also contribute to synaptic maladaption and/or cognitive dysfunction in adolescent toluene abusers.

Conflict of interest

There is no conflict of interest.

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