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Adolescent ethanol exposure: does it produce long lasting electrophysiological effects?

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Abstract

This review discusses evidence for long lasting neurophysiological changes that may occur following exposure to ethanol during adolescent development in animal models. Adolescence is the time that most individuals first experience ethanol exposure and binge drinking is not uncommon during adolescence. If alcohol exposure is neurotoxic to the developing brain during adolescence, not unlike it is during fetal development, then understanding how ethanol affects the developing adolescent brain becomes a major public health issue. Adolescence is a critical time period when cognitive, emotional and social maturation occurs and it is likely that ethanol exposure may affect these complex processes. In order to study the effects of ethanol on adolescent brain animal models where the dose and time of exposure can be carefully controlled that closely mimic the human condition are needed. The studies reviewed provide evidence that demonstrates that relatively brief exposure to high levels of ethanol, via ethanol vapours, during a period corresponding to parts of adolescence in the rat is sufficient to cause long-lasting changes in functional brain activity. Disturbances in waking EEG and a reduction in the P3 component of the ERP have been demonstrated in adult rats that were exposed to ethanol vapour during adolescence. Adolescent ethanol exposure was also found to produce long lasting reductions in the mean duration of slow-wave sleep (SWS) episodes and the total amount of time spent in SWS, a finding consistent with a premature aging of sleep. Further studies are necessary to confirm these findings, in a range of strains, and to link those findings to the neuroanatomical and neurochemical mechanisms potentially underlying the lasting effects of adolescent ethanol exposure.

Keywords

Adolescence; EEG; ERPs; Ethanol; Sleep

Adolescence a developmental epoch at high risk for initiation of ethanol use

Adolescence is a developmental period of enormous strength and resilience. As compared to young children adolescents are bigger, faster, and stronger and are achieving the apex of their

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capacity to withstand cold, injury, heat, and physical stress and are achieving maturational improvements in reaction time, reasoning abilities and immune function (Arnett, 1999; Dahl, 2004; Tanner, 1989). Adolescence is also a time for an increase in the tendencies toward sensation seeking, risk taking and emotional/motivational changes that lead to an enhanced vulnerability to mortality and morbidity (Irwin and Millstein, 1991). It has been postulated that these sensation-seeking and risk taking behaviors while enhancing morbidity and mortality are also critically important in the facilitation of the adolescent transition to maturity. One theory posits that these behaviors have an evolutionary advantage through their ability to increase peer-directed interactions that may lead to enhanced reproductive fitness in offspring produced from genetically unrelated individuals (Bixler, 1992; Moore, 1992). This increase in risk-taking and sensation seeking behaviors combined with enhanced peer-directed interactions can also lead to experimentation with ethanol and drugs in our modern society (Martin et al., 2002).

The 2007 National Survey on Drug Abuse and Health reported that approximately 16% of teens between the age of 12 and 17 were current users of ethanol and 10% of these individuals were binge drinkers (U.S. Department of Health and Human Services, 2008). In many individuals, adolescence is the time when the developing brain is first exposed to potentially neurotoxic levels of ethanol. Given the prevalence of ethanol consumption among adolescents, especially binge drinking (U.S. Department of Health and Human Services, 2008), studies assessing the potential long term effects of adolescent ethanol exposure on functional brain activity and behavior are an important public health concern.

Adolescence, a unique vulnerability window to developmental consequences of ethanol exposure?

The idea that the developing brain is particularly sensitive to the potentially toxic effects of ethanol was first advanced by clinical reports describing deficits in the offspring of ethanol-abusing women (see Jones and Smith, 1973; Lemoine et al., 1968). Fetal alcohol spectrum disorders are characterized by physical anomalies, behavioral and cognitive deficits as well as a host of organ system defects (see Guerri et al., 2009; Hofer and Burd, 2009; Sokol et al., 2003) and may affect as many as 1% of all births (May and Gossage, 2001). The exact composition of the range birth defects seen following fetal ethanol exposure seen in an individual depend on a number of genetic and environmental factors but appear to be related to the time during development that the fetus was exposed.

Adolescence is also an important developmental period that is potentially vulnerable to the neurotoxic effects of ethanol (see Ref. Spear, 2000a for review). Adolescence is a critical time period for brain development when cognitive, emotional and social maturation occur. It has been suggested that adolescence is a developmental period when an individual achieves their level of social and emotional fluency (see Dahl, 2004). It has been further suggested that when this developmental process is interfered with (perhaps by ethanol exposure) this emotional learning process may be negatively impacted leading to social consequences. During adolescence there are also major changes that occur in brain morphology including the selective removal of 40–50% of the synapses (i.e. synaptic pruning) in cortical and subcortical brain regions (Johnston, 1995; Lidow et al., 1991; Seeman, 1999, van Eden, 1990), continued myelination of cortical regions (Giedd et al., 1996; Sowell et al., 1999), and dramatic changes in receptor levels and sensitivity (Gould et al., 1991; Lidow et al., 1991). In spite of these well documented changes in brain structure and function, compared to the study of fetal ethanol effects, few studies have assessed the long term effects of chronic drug or ethanol exposure on the brain or behavior during this crucial time during development (Trauth et al., 2000; White et al., 2000). It is known that the adolescent brain is highly sensitive to excitotoxic insult, particularly in cortical and hippocampal regions (Johnston, 1995). Given that repeated exposure to and withdrawal from ethanol can produce increased neural excitability and

excitotoxic cell death (Chandler et al., 1993; Ehlers and Chaplin, 1991; Hunter et al., 1978; Rudolph et al., 1998; Smothers et al., 1997; Veatch and Gonzalez 1996), we hypothesized that adolescent ethanol exposure would have profound and long-lasting effects on measures of neurophysiological function.

Electrophysiological assessment of developmental changes during adolescence in humans

Dramatic changes in the neurophysiology of the brain have also been noted during adolescent development in humans (Niedermeyer, 1999; Pearce et al., 1989). One electrophysiological measure that has been intensively studied in human subjects to assay ethanol effects, ethanol related risks and vulnerability to several mental disorders is the P300 or P3 component of the event-related potential (ERP) (see Bauer and Hesselbrock, 1999a, 1999b; Begleiter and Porjesz, 1999; Hansenne and Ansseau, 1999; Hill et al., 1999a; Mathalon et al., 2000; Polich et al., 1994; Porjesz et al., 2005). The P3 is a positive going potential with a latency of about 300 msec when it is elicited by auditory stimuli in normal young adults (Donchin et al., 1986; Sutton et al., 1965). The component can be identified from averaged electroencephalographic (EEG) waveforms, and while the exact cognitive concomitants of the P3 are not certain, it reliably occurs after “unexpected” or “task relevant” events (Donchin and Coles, 1988; Polich, 1987, 1999; Polich and Kok, 1995; Verlerger, 1988).

Over the course of adolescence the P3 component of the ERP is modified, with P3 latency decreasing with age, and P3 amplitude tending to become larger (Polich et al., 1990). Both the waking and sleeping EEG also go through large changes in amplitude and frequency characteristics during this time period. The posterior alpha rhythm in the adolescent brain is characterized by a higher EEG amplitude and increases in EEG frequency (see Niedermeyer and Lopes da Silva, 1999). There is also evidence of a decline in slower waves over time in the waking EEG (see Niedermeyer and Lopes da Silva, 1999).

Evaluation of the sleep of adolescents, compared to adults, has revealed higher slow-wave sleep (SWS) amplitudes and which, overall, the percentage of SWS is significantly negatively correlated with age (Ohayon et al., 2004). Sleep difficulties have been reported to be not uncommon in human adolescents and furthermore, poor or inadequate sleep has been shown to be associated with negative outcomes in adolescents including emotional dysfunction and behavioral problems (Mindell and Meltzer, 2008; Roberts et al., 2002). These findings undoubtedly reflect some of the neuroanatomical and neurochemical changes occurring during the adolescent period. Therefore, electrophysiological assessment using EEG measures of waking and sleeping as well as ERP techniques could potentially provide a functional link between the neuroanatomical, neurochemical, and behavioral effects of adolescent drug exposure.

Electrophysiological consequences of adolescent ethanol exposure in humans

While electrophysiology has been successfully used to assess the chronic effects of long-term ethanol usage (Begleiter and Platz, 1972; Porjesz et al., 2005), its role to assay the effects of adolescent ethanol exposure has been limited. Previous studies demonstrating a decrease in P3 amplitude in youths at high risk for substance use disorder have proposed that the reduction in P3 amplitude is due to impaired inhibitory regulation, also known as “disinhibition” (see Bauer and Hesselbrock, 2003; Begleiter et al., 1984; Berman et al., 2006; Habeych et al., 2005; Hill et al., 1995; Iacono et al., 2002; Tremere and Pinaud, 2006). These results are consistent with previous reports by Hill and colleagues suggesting that the reduction in P3 amplitude seen in children at high risk for developing ethanol dependence is due to a developmental delay that

can be seen in adolescents and children, but not in adults (Hill and Shen, 2002; Hill et al., 1999b).

We recently investigated ERPs in young adult Southwest California Indians (SWC) who had a history of binge drinking during their adolescence (Ehlers, et al., 2007). Findings from this study showed that lower P450 amplitude was associated with adolescent ethanol exposure, and family history of ethanol dependence was a significant covariate in the analyses. In contrast, we did not find a reduction in P3 amplitude in older SWC Indians as a function of family history of ethanol dependence, only as a function of a personal history of ethanol dependence (Criado and Ehlers, 2007). In this study, we also found that decreases in the latency of the P3 component in response to a facial expression task were associated with a history of adolescent ethanol exposure in SWC Indian young adults. These findings contrast previous studies that have reported increases in P3 latency as a function of ethanol dependence, particularly in older adults (Biggins et al., 1995; Pfefferbaum et al., 1987). Since the visual P3 decreases in amplitude and latency over the course of adolescence and stabilizes during young adulthood (e.g., Hill and Shen, 2002), adolescents exposed to ethanol may be experiencing a more rapid maturation of their age-related changes in P3 latency (Ehlers, et al., 2007). Overall, these results suggest that a high risk for ethanol dependence in adolescents and a personal history of adolescent ethanol exposure produce differential effects on P3 amplitude and latency. Further research is needed to characterize the mechanisms mediating these differential effects on the P3 ERP component. These preliminary studies are an important step in determining the neurophysiological consequences of adolescent binge drinking in adult humans.

Evidence from human studies may provide insight into the consequences of chronic ethanol exposure on sleep. The effects of adolescent ethanol exposure on sleep have not been well studied. In contrast, the effects of ethanol on sleep have been extensively characterized in adults (Roehrs and Roth, 2001). In a previous study, we found an increase in the EEG peak frequencies in ethanol-dependent individuals in recovery (Irwin et al., 2000). Moreover, we have also shown greater slow-wave frequencies also occur as a normal function of normal aging (Ehlers and Kupfer, 1989). These findings, coupled with our results in adolescent ethanol exposed rats described in the next sections, have led us to suggest that the aging process of the sleep EEG may be accelerated as a consequence of adolescent chronic exposure. A recent study characterized sleep changes following cessation of marijuana and ethanol use during late stages of adolescence (Cohen-Zion et. al., 2009). This study found that past month ethanol use, but not marijuana intake, predicted the percent of rapid eye movement (REM) sleep when recorded during the second night of abstinence (Cohen-Zion et. al., 2009). These findings were not observed by day 28 of abstinence. In contrast, studies in adult chronic ethanol users showed that abnormal changes in sleep patterns can persist for up to two years following last use (Drummond et al., 1998). These data suggest that changes in sleep patterns associated with adolescent ethanol use may subside within several weeks of abstinence. Further research will be required to determine if adolescent ethanol exposure causes a premature aging of sleep, but the similarities between adolescent exposures and aging merit further investigation.

Using animal models to study electrophysiological effects of adolescent ethanol exposure

Adolescence, in the rodent, has many similarities to the human condition making it a good model to study the effects of periadolescent drug exposure (Spear, 2000b; 2000c; Spear and Varlinskaya, 2005). However, adolescence is difficult to precisely delineate as it is a transitional developmental period without distinct boundaries (Spear, 2000a). Spear and Brake (1983) have suggested that periadolescent studies in the rodent should include some portion of postnatal days 28–42, as many behavioral and neural changes attributed to the transition through adolescence can be observed within these boundaries in rats. During this

periadolescent period, there is increased social interaction, play, exploration, and locomotor activity (Spear, 2000a; Varlinskaya et al., 1999). Further, the rodent brain undergoes continued myelination, synaptic pruning, and alterations in receptor binding and sensitivity in various neurotransmitter systems during this time (Gould et al., 1991; Hamano et al., 1996; Nunez et al., 2000; Nurse and Lacaille, 1999; Teicher et al., 1995), as has been reported in other species during adolescence. These central nervous system changes are hypothesized to influence functional activity in the hippocampus (Dumas and Foster, 1998; Nurse and Lacaille, 1999; Swartzwelder et al., 1995a) and amygdala (Terasawa and Timiras, 1968).

Animal models of ERPs have been developed in order to further explore the neurophysiological basis of the P3 and other ERP components. Several studies have reported that late positive components could be generated in rats (Ehlers et al., 1991; Hurlbut et al., 1987; Jodo et al., 1995; O'Brien, 1982; Shinba, 1997; Takeuchi et al., 2000; Yamaguchi et al., 1993). Most of these studies have recorded P3's in animals from electrodes overlying cortical sites; however, some studies have also identified P3's in recordings from temporal lobe sites such as hippocampus and amygdala (Ehlers and Chaplin, 1991; Ehlers et al., 1998; Shinba et al., 1996).

It is important to note that EEG and ERPs have proven useful in assessing the acute and chronic effects of ethanol following prenatal and adult exposure in both humans and rodents (Ehlers and Chaplin, 1991; Kaneko et al., 1993, 1996a, 1996b; Scher et al., 1998, Slawecki et al., 1999). It is therefore reasonable to suggest that these same variables should prove useful in assessing the consequences of adolescent ethanol exposure.

Effects of adolescent ethanol exposure on ERPs in rodents

We have used an ethanol exposure paradigm that involves placing rats in ethanol vapour chambers during their adolescence and then testing them as adults for any long lasting neurophysiological effects. Although ethanol exposure through respiration does not mimic drinking in adolescent humans it does produce precise and stable blood ethanol levels (175-250 mg%) (see Slawecki et al., 2001) that are difficult to achieve in rodents drinking ethanol that are not selectively bred for high ethanol drinking. Moreover, our laboratory has used this technique to study the neurophysiological consequences of adolescent and adult ethanol exposure (e.g., Criado et al., 2008a, 2008b; Ehlers and Slawecki, 2000; Slawecki, 2002; Slawecki et al., 1999, 2000a, 2000b, 2001). Using this paradigm, we have investigated the effects of this ethanol exposure on ERPs. In that study, male Sprague-Dawley rats were exposed to ethanol vapour for 5 days (PN day 35-40) or 10 days (PN days 30-40) for 12 h/day. EEG and ERPs were then assessed at 6-7 weeks post ethanol exposure. Ethanol exposure for 10 days, but not for 5 days, was found to reduce the P3 amplitude of the ERP generated by an auditory oddball paradigm in the dorsal hippocampus. Ten day ethanol exposure was also found to reduce the amplitude of the P2 component of the ERP in both hippocampus and in cortex.

The effects of adolescent ethanol exposure on P2 amplitude are consistent with previous reports of ethanol-induced decreases in cortical and hippocampal P2 amplitude seen following adult exposure to ethanol by vapour (Ehlers and Chaplin, 1991; Slawecki et al., 1999). In our previous studies in adult rats (Ehlers et al., 1998; Slawecki et al., 2000a), decreases in P2 latency and amplitude have been observed when the reinforcement contingencies associated with a conditioned stimulus are extinguished. Thus, it could be hypothesized that the reduction seen in P2 waves following adolescent ethanol exposure may indicate the presence of brain deficits in processes associated with learning and memory. Ethanol exposure during adolescence was also found to decrease hippocampal P3 amplitudes. A decrease in hippocampal P3 amplitude could partially result from excitotoxicity associated with repeated ethanol withdrawals. Previous studies in rats have demonstrated that exposure to high levels of ethanol can induce

cell death in the hippocampus (Walker et al., 1980; West et al., 1986). Additionally, recent magnetic resonance imaging studies have demonstrated that hippocampal volume is significantly decreased, in adolescents and young adults with ethanol use disorders (De Bellis et al., 2000). Reductions in P3 amplitude have also been reported in children with Fetal Alcohol Syndrome (Kaneko et al., 1996a). Overall, these data are consistent with previous reports that have suggested that the developing hippocampus is very sensitive to neurotoxic insult (Chan et al., 1998; Roy and Sabherwal, 1998; West et al., 1986).

The differential sensitivity to ethanol that is seen during development is most likely the result of changes in many brain systems, including GABAergic and glutamatergic systems (Acheson et al., 1999; Little et al., 1996; Swartzwelder et al., 1995b) that occur over the course of adolescence. Cortical and hippocampal sensitivity to excitotoxic cell death occurs during this time (Johnston, 1995), and thus it seems probable that glutamate neurotoxicity could play a role in the ERP effects seen following adolescent ethanol exposure. P3 amplitude in the hippocampus has been demonstrated to be sensitive to altered glutamatergic function, as administration of MK-801 has been found to produce decreases in the amplitude of the rat hippocampal P3 (Ehlers et al., 1992). Consistent with these findings, studies characterizing the cellular and molecular mechanisms underlying the enhanced vulnerability to ethanol exposure during adolescence have frequently focused on studying glutamatergic neurotransmission (see Crews et al., 2002; Fadda and Rossetti, 1998), and in particular the *N*-methyl-D-aspartate (NMDA) type of glutamate receptor. We recently determined the role of of NMDA receptors in the development of long-term compensatory neurophysiological changes following adolescent ethanol exposure (Criado et al., 2008a). In this study, adolescent rats were exposed to a chronic period of ethanol exposure (5 weeks) and the role of NMDA receptors in the expression of compensatory neurophysiological changes were assessed after a prolonged withdrawal period (8 weeks). Evaluation of ERPs suggests that ethanol-exposed rats showed increased sensitivity to the effects of MK-801 reducing N1 and P1 latencies and P1 amplitude in ethanol-exposed rats. These data suggest neuroadaptive changes in NMDA-mediated regulation of these ERP components following adolescent ethanol exposure. Our findings showed that MK-801 significantly reduced P3 ERP amplitude and increased P3 ERP latency in control, but not in ethanol-exposed rats. Earlier evidence showing that acute administration of MK-801 significantly reduces hippocampal P3 amplitude in the rat suggests an important role of the glutamatergic NMDA system in the generation of the P3 ERP (Ehlers et al., 1992). In fact, reduction in hippocampal P3 amplitudes have been suggested to partially contribute to the long-lasting learning and memory deficits following chronic ethanol exposure (Arendt et al., 1989; Beracochea et al., 1992). Therefore, these data suggest that NMDA-mediated regulation of P3 amplitude is disrupted following adolescent ethanol exposure. Whether the lack of NMDA-mediated regulation of P3 amplitude is due to glutamate neurotoxicity following adolescent ethanol exposure is presently unknown. These results provide evidence suggesting that adolescent ethanol exposure produces complex long-lasting effects increasing and decreasing the efficacy of NMDA systems regulating cortical and hippocampal ERPs.

There is evidence to suggest that NMDA receptors mediate the induction of hippocampal long-term potentiation (LTP) and their activation is required for hippocampal-dependent learning tasks (e.g., Bliss and Collingridge, 1993; Sakimura et al., 1995; Villarreal et al., 2002). Moreover, cortical and hippocampal NMDA receptors play an important role regulating cognitive processes that are impaired by adolescent ethanol exposure (Carpenter-Hyland and Chandler, 2007; Crews et al., 2007; Krystal et al, 2003; Robbins and Murphy, 2006). In view of the well-documented evidence on the effects of ethanol on hippocampal physiology and hippocampal-dependent learning (see Matthews and Morrow, 2000) and findings from our previous studies, NMDA receptors may play an important role in the short- and long-term consequences of adolescent ethanol exposure. Adolescence has been found to be characterized

by a transient overproduction of NMDA receptors (e.g., Insel et al., 1990). Findings from several electrophysiological studies have provided evidence for interactions between NMDA receptors and ethanol during adolescence. Electrophysiological studies have demonstrated age-related differences in the sensitivity of those NMDA receptors to the acute and chronic effects of ethanol exposure. In those studies the inhibitory effects of ethanol on NMDA-mediated cortical post-synaptic currents, hippocampal LTP, excitatory post-synaptic potentials, and on the hyperpolarization activated cation current (I_h) in hippocampal GABAergic interneurons have been found to be more pronounced in adolescent rats compared to adult rats (Li et al., 2002; Pyapali et al., 1999; Swartzwelder et al., 1995b; Yan et al., 2009). Additionally, there is evidence to demonstrate that a compensatory upregulation of NMDA systems may occur following prolonged ethanol exposure and withdrawal (Carpenter-Hyland and Chandler, 2007). These findings are consistent with previous reports characterizing the effects of adolescent ethanol exposure on hippocampal-dependent spatial memory. Previous studies have shown that adolescent ethanol exposure produces tolerance to the deficits in spatial memory produced by acute ethanol (Silvers et al., 2003). More recently, it was demonstrated in vivo single-cell tolerance to an acute ethanol challenge in young adult rats following adolescent ethanol exposure (Tokunaga et al., 2006).

While there is evidence to suggest protracted changes in NMDA systems following adolescent ethanol exposure, it is still not clear whether the compensatory changes in NMDA systems after adolescent ethanol exposure described above were triggered during chronic ethanol exposure or during the prolonged withdrawal period. We previously suggested that the age-related differential effects of ethanol exposure are likely due to developmental changes in the adolescent brain (Slawecki et al., 2001). However, it is likely that NMDA-mediated neuroadaptive changes and neurotoxicity during ethanol withdrawal also account for some of those findings. Previous behavioral studies have shown that during ethanol withdrawal, ethanol-dependent rats are more susceptible to the pro-convulsant effects of NMDA (Sanna et al., 1993). Enhanced NMDA activity have been associated to several behavioral and neurophysiological characteristics of ethanol withdrawal, including irritability and anxiety (Erden et al., 1999), increased seizure susceptibility (Erden et al., 1999; Morrisett et al., 1990; Sanna et al., 1993), and neurophysiological hyperarousal (Grover et al., 1998; Nelson et al., 1999). Further studies are necessary to determine the impact of adolescent ethanol exposure on brain neurotransmitter systems and to relate those changes to electrophysiology and behavior.

Effects of adolescent ethanol exposure on EEG and sleep in rodents

The effects of adolescent ethanol exposure, through the use of ethanol vapours, have also been used to explore the effect of such exposure on waking and sleeping EEG. Exposure to ethanol vapours for 10 days from PD 30 to PD 40 was found to produce significant increases in spectral power in the 1–2 Hz frequency range in the parietal cortex EEG and the 16–32 Hz range in the hippocampal EEG during waking (Slawecki et al., 2001). The presence of only a few long-term effects of ethanol on the EEG is consistent with previous studies that have demonstrated only transient and subtle effects of prolonged ethanol exposure on the adult waking EEG (Ehlers and Chaplin, 1991; Slawecki et al., 2000a). For example, the EEG normalizes after only two weeks when exposed to ethanol vapour continuously for 28 days in adult studies (Ehlers and Chaplin, 1991). This may indicate that the mechanisms regulating the waking EEG in rats are less sensitive to ethanol-induced disruption or they are better able to compensate for the deleterious effects of chronic ethanol exposure.

Findings from our previous study showed pronounced increases in high frequency parietal EEG power (16-32 and 32-50 Hz) during adolescent ethanol withdrawal (7-10 h after termination of ethanol exposure) (Slawecki et al., 2006). More recently, we found that

adolescent ethanol vapour exposure produced no significant effects on baseline parietal EEG power assessed 5 weeks post-ethanol exposure (Criado et al., 2008a). These data suggest that changes in parietal EEG power following adolescent ethanol exposure are likely normalized after a prolonged withdrawal period. Our findings also provide evidence of complex compensatory changes in EEG measures of NMDA receptor function after 5 weeks of adolescent exposure to ethanol vapours (see Criado et al., 2008a). Significantly different EEG responses were found in response to systemic administration of MK-801 in the ethanol vapour exposed rats compared to controls. However, significantly reduced parietal EEG power in the 4-6, 6-8, 8-16 and 16-32 Hz frequency bands were found following MK-801 administration in the rats exposed to ethanol vapour during adolescence, but not in the control rats. These data suggest that a compensatory upregulation of NMDA systems following prolonged adolescent ethanol exposure and withdrawal may influence these EEG frequency bands. It is also possible that NMDA-mediated neuroadaptive changes and neurotoxicity during ethanol withdrawal may also account for EEG changes in response to MK-801 seen in adolescent vapour exposed rats. For instance, enhanced NMDA activity has been associated with several of the behavioral and neurophysiological characteristics of ethanol withdrawal, including irritability and anxiety (Erden et al., 1999), increased seizure susceptibility (Morrisett et al., 1990), and neurophysiological hyperarousal (Nelson et al., 1999). Further studies will be necessary to determine the mechanisms underlying these findings of EEG changes following adolescent ethanol exposure.

The effect of adolescent ethanol exposure, produced by ethanol vapours, also appears to have a profound impact on the rat sleeping EEG. In one of our studies we found protracted alterations in sleep in adult rats exposed to prolonged ethanol vapours during adolescence (see Criado et al., 2008b). In that study, adolescent male Wistar rats were exposed to ethanol vapours for 12 h/day for 5 weeks. Sleep EEGs were obtained during a 4-h recording sessions in adult animals after 5 weeks of withdrawal from the ethanol vapours. Adolescent ethanol exposure significantly reduced the mean duration of slow-wave sleep (SWS) episodes and the total amount of time spent in SWS in ethanol vapour exposed rats as compared to the controls. Spectral analysis of the EEG also revealed that adolescent ethanol exposure significantly increased cortical peak frequencies during SWS in the 2-4, 4-6, and 6-8 Hz bands in adult rats. There is considerable evidence to suggest that variations in cortical peak frequencies correlate with cognitive performance and have been associated with attentional demands and arousal (Angelakis et al., 2004; Klimesch et al., 1990). However, correlations of cortical peak frequencies with high ethanol consumption have not consistently correlated in rodent models of high ethanol consumption, compared to their low drinking counterparts (e.g., Katner, et al., 2002; Morzorati, et. al., 1994; Robledo, et al., 1994; Slawecki et. al., 2000b, 2001, 2003). These data suggest that unique electrophysiological characteristics may index ethanol preference in each model of high vs. low ethanol consumption.

The neurobiological mechanisms that underlie abnormalities seen in SWS in rats exposed to chronic ethanol vapours during adolescence are not known. As we previously described, studies characterizing the cellular and molecular mechanisms mediating the enhanced vulnerability to ethanol exposure during adolescence have focused on studying glutamatergic neurotransmission and the NMDA glutamate receptor (Carpenter-Hyland and Chandler, 2007; Crews et al, 2002, 2007). However, it is still unclear whether lasting neuroadaptive changes of NMDA-mediated activity during adolescent ethanol exposure and withdrawal could be mediating their compensatory effects on SWS. The mechanisms by which changes in NMDA receptor function mediate the consequences of adolescent ethanol exposure on SWS are complex and involve multiple neural circuits and neurotransmitters regulating several stages of the sleep-wake cycle. For instance, glutamate-containing neurons are the main component of the cortical-activating and behavioral-arousal systems in the CNS and play a variety of roles, from facilitating postural muscle tone to stimulating cortical activation

(reviewed by Jones, 2005). Moreover, glutamate neurotransmission is primarily associated with arousal, rather than sleep promotion. These arousal-promoting glutamatergic pathways are also regulated by sleep-promoting GABAergic-containing neurons in regions such as the brainstem and thalamus. GABAergic projections have been shown to inhibit glutamate-containing neurons in the brainstem reticular formation and thalamocortical projection relay to suppress cortical activation (Maloney et al., 1999, 2000; Steriade et al., 1994). There is electrophysiological evidence to suggest an increased sensitivity of GABAergic neurotransmission to ethanol during adolescence (Fleming, et al., 2007; Li, et al., 2003). Therefore, ethanol-induced changes in the regulation of glutamate cortical-activating systems by GABAergic sleep-promoting neurons during adolescence may also partially account for the effects of adolescent ethanol exposure on adult SWS.

Summary and questions for future developments

This review discusses evidence for long lasting neurophysiological changes that may occur following exposure to ethanol during adolescent development in animal models. If ethanol exposure is neurotoxic to the developing brain during adolescence, not unlike it is during fetal development, then understanding how ethanol affects the developing adolescent brain becomes a major public health issue. Adolescence is a critical time period when cognitive, emotional and social maturation occurs and it is likely that ethanol exposure may affect these complex processes. In order to study the effects of ethanol on adolescent brain animal models the dose and time of exposure must be carefully controlled to closely mimic the human condition.

The studies reviewed provide evidence that demonstrates that relatively brief exposure to high levels of ethanol, via ethanol vapours, during a period corresponding to parts of adolescence in the rat is sufficient to cause long-lasting changes in functional brain activity. These long-lasting effects of adolescent ethanol exposure likely involve many brain systems and are due, in part, to developmental differences in the sensitivity to ethanol. The inhibitory effects of ethanol are more pronounced in adolescent rats compared to adult rats and these developmental differences appear to be mediated by GABAergic and glutamatergic systems. NMDA-mediated post-synaptic currents in cortical neurons, the I_h current in hippocampal GABAergic interneurons and hippocampal LTP are some examples of NMDA and GABAergic mechanisms showing developmental differences in the sensitivity to ethanol.

Disturbances in waking EEG and a reduction in the P3 component of the ERP have been demonstrated in adult rats that were exposed to ethanol vapour during adolescence. The decrease in P3 amplitude may indicate the presence of brain deficits in processes associated with learning and memory. Adolescent ethanol exposure has been shown to produce long-lasting changes in the efficacy of NMDA systems regulating cortical and hippocampal ERPs. Consistent with these observations, disturbances in parietal EEG power following adolescent ethanol exposure may be mediated by compensatory upregulation of NMDA systems. There is evidence to suggest that adolescent ethanol exposure produce long lasting reductions in the mean duration of SWS episodes and the total amount of time spent in SWS, a finding consistent with a premature aging of sleep. The mechanisms mediating the long-term effects of adolescent ethanol exposure on SWS may involve GABAergic sleep-promoting neurons that regulate glutamatergic cortical-activating systems.

There are several open questions that must be answered in order to fully interpret these findings and to extend them to future studies. Adolescence is a window in time when brain and behavior are relatively “plastic”. Thus, exposure to ethanol during this time may be more toxic as these studies suggest or it may be that some aspects of the brain can recover over time even more than adult or fetal exposure. We do not know if there are critical windows within the adolescent period that are more or less vulnerable to ethanol exposure. We do not know if there are

threshold doses of ethanol that are necessary in order to produce long lasting changes in brain function. Further studies are also necessary to determine exactly how long lasting the effects reported are. In our studies, and in many others, only male animals have been studied thus we do not know if female animals are more or less vulnerable to the effects of adolescent ethanol exposure. Additionally, many studies have used Sprague-Dawley rats in their investigations and therefore we do not know if one or another strain of rats is more or less susceptible to the toxic effects of ethanol during adolescence. Additionally, most studies have investigated the effects of adolescent ethanol exposure alone when in fact during adolescence many users also get exposed to nicotine and marijuana as well as other drugs. Thus, studies are necessary that will evaluate the effects of multi-drug exposures. We need to know the exact brain structures and mechanisms that are sensitive to adolescent ethanol exposure and ones that are resilient. Additionally, we need to link studies of these brain mechanisms to behavior and affect. Since controlled studies of adolescent ethanol exposure are not ethically possible in humans we will need to continue this clinically relevant work in a host of animal models.

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