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Contribution of early environmental stress to alcoholism vulnerability

Joannalee C. Campbell[a], **Karen K. Szumlinski**[a,b], and **Tod E. Kippin**[a,b,*]

[a]Department of Psychology, University of California, Santa Barbara, CA 93106-9660, USA

[b]Neuroscience Research Institute, University of California, Santa Barbara, CA 93106-9660, USA

Abstract

The most problematic aspects of alcohol abuse disorder are excessive alcohol consumption and the inability to refrain from alcohol consumption during attempted abstinence. The root causes that predispose certain individuals to these problems are poorly understood but are believed to be produced by a combination of genetic and environmental factors. Early environmental trauma alters neurodevelopmental trajectories that can predispose an individual to a number of neuropsychiatric disorders, including substance abuse. Prenatal stress (PNS) is a well-established protocol that produces perturbations in nervous system development, resulting in behavioral alterations that include hyperresponsiveness to stress, novelty, and psychomotor stimulant drugs (e.g., cocaine, amphetamine). Moreover, PNS animals exhibit enduring alterations in basal and cocaine-induced changes in dopamine and glutamate transmission within limbic structures, which exhibit pathology in drug addiction and alcoholism, suggesting that these alterations may contribute to an increased propensity to self-administer large amounts of drugs of abuse or to relapse after periods of drug withdrawal. Given that cocaine and alcohol have actions on common limbic neural substrates (albeit by different mechanisms), we hypothesized that PNS would elevate the motivation for, and consumption of, alcohol. Accordingly, we have found that male C57BL/6J mice subject to PNS exhibit higher operant responding and consume more alcohol during alcohol reinforcement as adults. Alterations in glutamate and dopamine neurotransmission within the forebrain structures appear to contribute to the PNS-induced predisposition to high alcohol intake and are induced by excessive alcohol intake. Accordingly, we are exploring the interactions between neurochemical changes produced by PNS and changes induced by consumption of alcohol in adulthood to model the biological bases of high vulnerability to alcohol abuse.

Keywords

Alcohol; Alcoholism; Addiction; Prenatal stress; Development; Vulnerability

Introduction

Alcohol is one of the most widely abused drugs with approximately 14% of the general American population meeting criteria for alcohol dependence (American Psychiatric Association, 2000). A major problem involved in alcohol abuse disorder is excessive alcohol intake, which results in a range of consequences, including memory loss, blackouts, loss of

* Corresponding author. Department of Psychology, University of California, Santa Barbara, CA 93106-9660. Tel.: +1-805-893-2459; fax: +1-805-893-4303. kippin@psych.ucsb.edu (T.E. Kippin).

consciousness, as well as damage to a number of organs, including the brain. A second major problem involved in alcohol abuse disorder is relapse, which is the rapid return to drinking, particularly to excessive drinking, during periods of attempted abstinence. Extensive use of animal models of alcohol abuse has provided insights into the mechanisms of alcohol action, the factors that determine individual vulnerability to alcoholism, and produced a method of screening potential therapeutic compounds. The present review summarizes our knowledge of the impact of early environmental stress as a risk factor for alcoholism and proposes that enduring alterations in corticolimbic glutamate induced by these stressors may mediate the increased vulnerability to alcohol abuse.

Prenatal stress enhances sensitivity to stressors and psychomotor stimulant drugs

Environmental stimuli during gestation and the early postnatal period have complex effects on developmental processes, resulting in permanent alterations in nervous system structure and function. In humans, children of mothers who experienced stress during gestation or early life stress exhibit alterations in early motor development, anomalies in brain morphology, and an increased risk of developing a range of neuropsychiatric disorders, including attention-deficit hyperactivity disorder, schizophrenia, depression, sleep disturbances, cognitive dysfunction, increased anxiety, and substance abuse disorders (reviewed in Huizink et al., 2004; Seckl and Meaney, 2006; Weinstock, 2001, 2005). Extensive data from animal studies are consistent with such findings (reviewed in Huizink et al., 2004; Kofman, 2002; Seckl and Meaney, 2006; Weinstock, 2001, 2005; Welberg and Seckl, 2001): repeated maternal exposure to stress during the last week of gestation (prenatal stress [PNS]) induces behavioral sequelae including (but not limited to) neuroendocrine and behavioral hyperresponsiveness to stressors and novelty, increased anxiety, learning and memory impairments, altered circadian rhythm function, impaired sexual function, and enhanced responsiveness to the behavioral activating and reinforcing properties of drugs of abuse. Although human PNS effects appear to be more severe when the maternal stressor is present early in gestation (Glynn et al., 2001), the majority of the animal literature, particularly rodent models, relies on stress manipulations later in gestation. This shift in stress exposure relative to gestational milestones reflects the fact that human neural development is precocious compared with most other mammals (Clancy et al., 2001). As a comparison, the peak time of neuronal proliferation and migration occurs in the last trimester of rat development, whereas the equivalent burst occurs early in the second trimester for humans (Yager and Ashwal, 2009), requiring a substantial shift in stressor timing for rodent models to replicate the impact of stress on that aspect of human brain development.

Of particular interest is the increased risk of substance abuse disorders after early environmental stress. In rodent models, PNS increases the initial locomotor response to amphetamine, enhances sensitization to the locomotor effects of amphetamine, and increases amphetamine intake and operant responding during amphetamine reinforcement (Deminiere et al., 1992; Henry et al., 1995). We have found that PNS in rats increases the locomotor responsiveness to cocaine (in both cocaine-naive and -experienced individuals). Although PNS rats do not differ from controls regarding the amount of cocaine self-administered intravenously in standard operant procedures, these rats exhibit higher levels of cocaine seeking under extinction conditions and after a noncontingent cocaine-priming injection (Kippin et al., 2008). Similarly, studies using separation of offspring from their mothers during the early postnatal period have found that prolonged (3–6 h) episodes of neonatal separation produce heightened responsiveness to stressors similar to that observed with PNS. In contrast, brief (10–15 min) episodes of neonatal separation, which elicit increased maternal behavior directed toward the offspring, produce lowered responsiveness to

stressors opposite to that observed with PNS in some studies (for reviews, see, e.g., Francis et al., 1996; Gutman and Nemeroff, 2002; Lehmann and Feldon, 2000). Moreover, prolonged postnatal separation produces enhanced cocaine self-administration and increased reinstatement of cocaine-seeking behavior (see, e.g., Flagel et al., 2003; Kosten et al., 2000; Lynch et al., 2005, but see also Matthews et al., 1999; Moffett et al., 2007). Thus, there are generally consistent findings supporting the notion that early life stress in animals can effectively model the heightened addiction vulnerability in humans subjected to adverse early life events.

PNS and alcohol reward

In contrast to the large amount of information available on the effects of PNS on stress and stimulant drug responsiveness, there is limited information regarding the impact of PNS on responsiveness to alcohol and alcohol intake. Although there are no studies definitively linking prenatal stress and vulnerability to alcoholism, large-scale studies documenting the impact of stress imposed by recent natural disasters (e.g., King and Laplante, 2005; Weems and Overstreet, 2008) on a variety of behavioral, cognitive, and mental health dimensions offer an opportunity to track the impact of time-specific early stressors on addiction vulnerability to a wide range of substances, including alcohol. Nevertheless, some studies have linked adverse early life events to a lack of resilience and that to later alcoholism (reviewed in Enoch, 2006; Tiet et al., 1998; Zimmermann et al., 2007; Zuker et al., 2008). However, it remains unclear if this propensity toward alcoholism reflects a specific vulnerability or general vulnerability to neuropsychiatric disease, as reflected by high comorbidity with other disorders (e.g., Cornelius et al., 2003; Krystal et al., 2006; Kushner et al., 2000; Schuckit, 2006).

Moreover, there are many behavioral components known to be influenced by PNS, both in humans and in animal models, which are themselves linked to greater propensity toward alcohol abuse and alcoholism. PNS is linked to increased anxiety, impulsivity, and mood disorders (for reviews, Beydoun and Saftlas, 2008; Weinstock, 2008), whereas anxiety sensitivity, depression, and avoidance coping strategies are themselves all predictive factors for higher alcohol consumption and a higher likelihood of an alcohol use disorder (Holahan et al., 2001; Schmidt et al., 2007). Two studies have reported that PNS blunts initial alcohol-induced hypothalamus–pituitary–adrenal axis activation, ataxia, and hypothermia (DeTurck and Pohercky, 1987; Van Waes et al., 2006). These findings suggest that PNS may produce lower initial sensitivity to alcohol, which along with clinical research indicating that initial responsiveness to alcohol (and other *N*-methyl-D-aspartate [NMDA] receptor antagonists) correlates with alcoholism vulnerability (for reviews, Krystal et al., 2003; Schuckit et al., 2004) suggests that PNS may serve as a useful model to assess alcoholism vulnerability due to initial alcohol responsiveness. A recent study conducted by Darnaudery et al. (2007) examined the long-term effects of PNS and its interaction with stressors on voluntary alcohol intake during continuous access in adult male and female rats. Under basal conditions, PNS rats did not differ from controls in terms of free-access alcohol intake, but a subgroup of PNS females that displayed initial high preference for alcohol further increased their intake when subjected to intense stressors as adults, whereas stress-induced changes in intake were not observed in PNS females exhibiting an initial low preference for alcohol or in PNS males, regardless of their initial alcohol preference (Darnaudery et al., 2007). Additionally, prolonged maternal separation during the early postnatal period increases alcohol intake during adulthood (Gustafsson and Nylander, 2006; Gustafsson et al., 2005; Huot et al., 2001; Jaworski et al., 2005; Ploj et al., 2003; Roman et al., 2003), whereas intake is decreased after brief (10–15 min) episodes of neonatal separation in some (Jaworski et al., 2005; Ploj et al., 2003), but not all, studies (Lancaster, 1998; Weinberg, 1987). Thus, the limited existing evidence suggests that PNS or maternal separation

procedures that produce a similar endophenotype also produce increased vulnerability to alcoholism-related behaviors.

Importantly, prior studies have only assessed the impact of early environmental stress on alcohol intake in strains of rats that exhibit modest ingestion levels (e.g., averaging <5 g/kg/day of oral intake; Darnaudery et al., 2007; Gustafsson and Nylander, 2006; Roman et al., 2005), and thus, the use of animal models that exhibit higher basal intake in PNS experiments may facilitate modeling vulnerability to excessive alcohol consumption. Furthermore, previous studies have only examined alcohol intake under continuous access conditions and have not investigated the influence of early environmental stressors on subsequent alcohol intake under operant contingency, which facilitates assessment of the motivational processes involved in alcohol-seeking behavior.

Accordingly, our group has initiated experiments examining the impact of PNS on alcohol-reinforced operant behavior using C57BL/6J mice, which exhibit spontaneous high alcohol intake (>10 g/kg/day of oral intake) and high alcohol preference under a variety of experimental conditions (e.g., Fuller, 1964; Rodgers and McClearn, 1962). In our studies, pregnant dams are subjected to either no manipulations or repeated restraint stress (confinement to a small plastic tube for 1 h, three times per day, from E14 until delivery); then, the offspring remain with their mother until weaning at 21 days of age when they are separated in same-sex groups of three to four mice. Starting at 8 weeks of age, male mice are given access to an alcohol bottle (15% alcohol in water) or a water bottle in their home cage for 8 weeks. Under these conditions, we observed high levels of alcohol intake (greater than 12 g/kg/day) but no significant differences in these levels between PNS and control males (Campbell et al., 2009)—a finding consistent with that reported earlier in PNS rats (Darnaudery et al., 2007). However, when the mice are trained to press a lever in an operant chamber to receive alcohol reinforcement, substantial differences emerged between PNS and control males. Mice were initially trained to press a lever for oral sucrose reinforcement (20 μL of 15% wt/vol sucrose in water delivered into a small cup) for 15 min/day followed by a standard sucrose fading procedure (Samson, 1986) with oral ethanol (20 μL of 10% ethanol vol/vol in water delivered into a small cup) serving as the final reinforcer. Although the behavior of PNS and control male mice did not differ during sucrose reinforcement, PNS males responded on the active lever approximately 60% more than did controls and exhibited an approximate 137% increase in the amount of alcohol consumed during the operant session. These data indicate that, consistent with the higher operant responding for cocaine and amphetamine reported by our laboratory and others (as previously mentioned), PNS increases the motivation for, and intake of, alcohol when access is response contingent (Campbell et al., 2009). These data indicate that PNS procedures may be useful in elucidating factors contributing to the biological bases of high vulnerability to substance abuse, including alcoholism.

Future behavioral directions

The brief daily operant self-administration sessions used in our preliminary study of the effects of PNS on operant responding and alcohol intake in mice are temporally similar to “binge” models of excessive alcohol consumption that have been investigated elsewhere (see, e.g., Finn et al., 2005; Rhodes et al., 2005; Szumlinski et al., 2007), and thus, it is of interest to test PNS mice under these limited-access, response-noncontingent conditions as well. Furthermore, another major problem associated with alcoholism is its reoccurring nature that results in high levels of relapse during periods of attempted abstinence. Although current animal models have limitations (see for reviews, e.g., Epstein et al., 2006; Katz and Higgins, 2003), the propensity to relapse appears to be modeled by reinstatement of operant responding produced by reexposure to ethanol in a noncontingent fashion or “priming,”

exposure to stressors, or during reexposure to alcohol-paired cues after response extinction. Given the higher levels of reinstatement of cocaine seeking produced in PNS rats relative to controls (Kippin et al., 2008), it is also of interest to determine if higher reinstatement of alcohol seeking is produced by PNS in C57BL/6J mice. However, the mouse studies to date have inconsistently observed drug-primed reinstatement after either noncontingent alcohol or cocaine reexposure (Finn et al., 2008; Fuchs et al., 2003; Highfield et al., 2002; Kruzich, 2007; Soria et al., 2008), although, like rats (for reviews, see, e.g., Lê and Shaham, 2002; See, 2005), reexposure to drug-associated cues (Finn et al., 2008; Fuchs et al., 2003; Heidbreder et al., 2007; Highfield et al., 2002; Kruzich, 2007; Sanchis-Segura et al., 2006; Tsiang and Janak, 2006; Zghoul et al., 2007) or exposure to stressors (Newton et al., 2008; Soria et al., 2008) produces substantial reinstatement of cocaine- or alcohol seeking in mice, and these latter paradigms may provide an avenue for investigating the interactions between PNS and alcohol “relapse” behavior. Finally, the importance of subject's sex in determining the responsiveness to alcohol intake and seeking has also been examined recently. Sex differences have important influences on the development of alcoholism (reviewed in, e.g., Witt, 2007). Evidence from animal models suggests that females may be biologically disposed to high vulnerability to the effects of alcohol and to engage in higher intake (see, e.g., Barr et al., 2004; Bell et al., 2003, 2006; Lancaster and Speigel, 1992; Wiren et al., 2006). Furthermore, sex differences interact with early postnatal stressors in determining responsiveness to stressors in adulthood (see, e.g., McCormick et al., 1995) and to alcohol (Darnaudery et al., 2007; also reviewed in Roman and Nylander, 2005). Accordingly, future experiments should also address potential interactions between PNS and sex on alcohol-seeking behavior in operant and/or binge models.

PNS effects on the limbic circuitry mediating addiction-related behaviors

The limbic system, comprising interconnected cortical, amygdalar, hippocampal, and striatal components using monoamine and amino acid neurotransmitters, is implicated strongly in the behavioral effects of alcohol, as well as other drugs of abuse (Koob, 2003; Lapish et al., 2006; McBride and Li, 1998). Previous research in our laboratory revealed that PNS in rats increases the propensity to relapse in an animal model of cocaine addiction, and this enduring behavioral consequence of the stressful experience during development was found to be associated with alterations in basal and/or drug-stimulated changes in extracellular dopamine and glutamate within the prefrontal cortex (PFC) and nucleus accumbens (NAC) (Kippin et al., 2008). More specifically, PNS elevated basal and cocaine-induced increases in mesocorticolimbic dopamine that underwent greater sensitization after cocaine self-administration and withdrawal (Kippin et al., 2008). Similar results for both basal dopamine levels in the NAC and increases in NAC dopamine levels after amphetamine challenge in both adolescent and adult PNS rats have been recently reported by others (Silvagni et al., 2008). Conversely, PNS reduced basal NAC extracellular glutamate but enhanced cocaine-stimulated glutamate release in the NAC both before and after experience with cocaine self-administration (Kippin et al., 2008). Of note, the reduction in basal NAC glutamate and the rise in NAC glutamate in response to an acute cocaine challenge injection are two neuroadaptations observed typically in rodents with a history of repeated cocaine experience (e.g., for review, Kalivas et al., 2005). Such data suggest that PNS elicits enduring neurochemical abnormalities in limbic monoamine and glutamate transmission that might “presensitize” subsequent behavioral responsiveness to drugs of abuse.

Although discrepancies exist in the literature concerning the precise relationship between alcoholism vulnerability and limbic dopamine transmission (e.g., Boone et al., 1997; Gongwer et al., 1989; Katner and Weiss, 2001; Kiianmaa et al., 1995; McBride et al., 1986, 1995; Murphy et al., 1987; Smith and Weiss, 1999), accumulating evidence supports a potential link between limbic glutamate transmission and alcohol preference/consumption

observed in genetic animal models. Evoked cortical glutamate release is approximately 50% higher in P versus NP rats, and this release is enhanced by alcohol in P rats but not in their NP counterparts (McBride et al., 1986). Moreover, comparisons of low–alcohol-drinking Fischer 344 versus Lewis rats (Selim and Bradberry, 1996) and of low–alcohol-drinking DBA2/J versus C57BL/6J mice (Kapasova and Szumlinski, 2008) revealed an increased capacity of acute or repeated alcohol injections to increase NAC levels of glutamate in high– versus low–alcohol-consuming strains. Conversely, pharmacological or genetic manipulations of the glutamate system that reduce aspects of alcohol reward in rodent models of alcoholism (e.g., glutamate receptor antagonists or deletion of glutamate receptor–associated genes) prevent the capacity of alcohol to elevate NAC glutamate transmission (Lominac et al., 2006; Szumlinski et al., 2005b). The consequences of PNS on alcohol-stimulated limbic dopamine and glutamate transmission have yet to be assessed. However, the fact that PNS produces enduring neurochemical abnormalities within brain regions analogous to those exhibiting pathologies in alcoholic individuals (e.g., Moselhy et al., 2001; Volkow et al., 1990) raises the distinct possibility that the enhanced motivation of PNS mice to self-administer alcohol (Campbell et al., 2009) may be related to enduring effects of this early developmental manipulation on PFC–NAC glutamate transmission.

PNS and Homer proteins: a link to alcoholism vulnerability?

Glutamate receptors, in particular the NMDA subtype of ionotropic glutamate receptors, are pharmacological targets for alcohol in the brain (e.g., Lovinger et al., 1989; Minami et al., 1998). Glutamatergic signaling involves extensive networks of proteins that constitute the postsynaptic density of asymmetric synapses, which comprise several scaffolding proteins that serve to integrate signaling through multiple receptor subtypes (see, e.g., Sheng and Hoogenraad, 2007), including those involved in dopamine and glutamate signaling (e.g., Hara and Pickel, 2005; Trudeau, 2004; reviewed in Ferre et al., 2007). Thus, likely potential mechanisms for PNS-induced alterations in alcohol-related behavior (Campbell et al., 2009) are differences in glutamate receptors, as well as their related postsynaptic density signaling/scaffolding proteins. To this end, PNS produces increased NMDA receptor and group 3 metabotropic glutamate receptor expression (Barros et al., 2004; Berger et al., 2002), which may both contribute to the enhancement of cocaine-stimulated glutamate release exhibited by PNS rats in our neurochemical study (Kippin et al., 2008). Furthermore, we have initiated investigations into the potential molecular bases of PNS-induced mesocorticolimbic glutamate/dopamine alterations by examining the effect of PNS on the expression of Homer proteins, which are crucial to the coordination of glutamate signaling within the postsynaptic density (see, e.g., Shiraishi-Yamaguchi and Furuichi, 2007) and regulate basal, as well as drug-induced changes in, extracellular glutamate within the PFC and NAC (for review, Szumlinski et al., 2008). Indeed, PNS produces regionally specific changes in specific Homer proteins within the brain of preadolescent female rats: upregulated in PFC, hippocampus, and amygdala but downregulated in striatum (Ary et al., 2007), and studies are ongoing to extend these data to adult animals of both sexes. Although the relevance of PNS-induced changes in limbic Homer expression for the heightened motivation for cocaine and alcohol exhibited by PNS rodents (Campbell et al., 2009; Kippin et al., 2008) is a topic of intense investigation in our laboratories, we know from a series of studies conducted in inbred C57BL/6J and hybrid mice that abnormalities in PFC Homer1 versus Homer2 expression alters cocaine-seeking behavior and PFC glutamate transmission (Ary et al., 2008; Lominac et al., 2005; Szumlinski et al., 2005a). Moreover, cocaine- or alcohol-induced changes in NAC Homer expression, particularly that of the rodent-specific Homer2b isoform, actively regulate both the rewarding/reinforcing and neurochemical-sensitizing properties of these two drugs of abuse (for review, Szumlinski et al., 2008). Such data have led to the working hypothesis that early environmental insults, such as repeated maternal stress, produce enduring changes in the expression of Homers and associated

receptor molecules within limbic structures and that such changes increase vulnerability to the motivational properties of drugs and alcohol reward in adulthood.

Conclusions

Modeling early developmental trauma using the PNS procedure produces numerous neurobiological abnormalities within limbic structures of the brain that have implications for a host of neuropsychiatric conditions, including substance abuse and dependence. As observed for the psychomotor stimulant cocaine, PNS augments the motivational properties of alcohol when assessed in adulthood. Thus, early environmental insults, such as repeated maternal stress, can produce enduring changes in the function of neural circuits subserving goal-directed behaviors. Although the precise cellular and molecular underpinnings of the interactions between PNS and subsequent drug/alcohol exposure on brain function remain to be more completely characterized, the data to date support the use of PNS protocols to screen for potential targets involved in promoting or protecting against addiction/alcoholism vulnerability.

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