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Abstract

As has been repeatedly demonstrated, alcohol can exert deleterious morphological and physiological effects during early stages in development. The present review examines nonteratological links existing between alcohol and ontogeny. Human and animal studies are taken into consideration for the analysis of fetal, neonatal, infantile, adolescent, and adult responsiveness to the drug. Sensitivity to alcohol's chemosensory and postabsorptive properties, as well as learning and memory processes mediated by such properties, are examined from this developmental perspective. The studies under discussion indicate that, within each stage in development, we can trace alcohol-related experiences capable of determining or modulating alcohol seeking and intake patterns.

Keywords

alcohol; fetus; neonate; infant; adolescence; adulthood; chemosensory; reinforcement; lactation; social interactions; feeding

INTRODUCTION

Oral consumption of alcohol is accompanied by chemosensory perception of flavor which plays an important role in its acceptance and rejection in both humans and animal models. Three independent sensory systems—taste, olfaction, and chemosensory irritation—are involved in the perception of flavor. Alcohol is perceived as a combination of sweet and bitter tastes, retronasal odor volatiles and oral irritation (e.g., burning sensation), which vary as a function

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of its concentration (Bachmanov et al., 2003; Duffy et al., 2004; Kiefer, 1995; Lanier, Hayes, & Duffy, 2005).

Those of us involved in the study of alcohol use and abuse frequently confront, metaphorically speaking, the above mentioned sweet and bitter sensations when examining the deleterious effects of the drug. Recognizing the existence of a pathological entity such as alcoholism drives our efforts to understand its etiology, its progression and even defy the notion that a definite cure is unlikely. The sweet sensation that progressive knowledge on these matters can help clinical and societal courses of action is often masked by the bitter component of the metaphor: with each diagnosis of alcoholism we realize that the goal of primary prevention is far from being met.

The discovery that alcohol is a teratogen (Jones & Smith, 1973; Lemoine, Harousseau, Borteyru, & Menuet, 1968) broadened the spectrum of health-related problems related with this pharmacological agent. Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorders (Riley & McGee, 2005) illustrate that the negative consequences of alcohol are more diverse than originally thought. The bitter taste is again present whenever considering that the physical, cognitive, and emotional well-being of a person can be congenitally jeopardized. With these findings we also become aware of something not as obvious as it might sound; the problems related to alcohol experiences are not restricted to a particular stage in development. FAS and alcoholism allude to what can be considered the extreme poles of this developmental perspective and both phenomena also represent extreme outcomes of alcohol-derived experiences.

The epidemiological and clinical literature indicates that alcohol experiences are derived from different modes of exposure throughout ontogeny (Spear & Molina, 2005). For example, in some cultures alcohol soaked cotton or gauze pads are frequently placed over the abdomen of human neonates or infants with the goal of avoiding infections derived from the remainder of the umbilical cord or to treat stomach spasms (e.g., Dalt, Dall'Anucim Kaverda, Chemollo, & Chiandetti, 1991; Faas, Sponton, Moya, & Molina, 2000; Mancini, 2004). In using these practices, transdermal absorption of alcohol and inhalation of alcohol vapors can lead to high infantile blood alcohol concentrations (Choonara, 1994). As will be later discussed in detail, maternal alcohol drinking during breastfeeding is still highly prevalent and implies an alternative mode of early exposure to the drug (e.g., Giglia & Binns, 2006; Mennella, 1999; Pepino & Mennella, 2004). Finally, epidemiological data clearly reflect the high prevalence of alcohol use and abuse in both children and adolescents across most of the world (e.g., Ahlstrom & Osterberg, 2005; Johnston, Malley, & Bachman, 2005).

The present review analyzes specific experiences with the drug during different developmental stages and how these experiences can play a significant role in the structure of alcohol seeking or acceptance patterns. The article follows a chronological order. We begin with the near term fetus exposed to alcohol doses that are not sufficient to exert teratogenic effects (JCM). Neonatal and infantile experiences with the drug are then analyzed in terms of affinity for alcohol ingestion and sensitivity to the drug's reinforcing properties (NES). The third section focuses on lactation; emphasizing alcohol's effects on milk availability, early perception of alcohol's chemosensory properties and memories derived from alcohol-related nursing experiences (JAM). We then move to adolescence where the focus of attention is primarily related to the predisposition towards alcohol use and abuse and the mechanisms that seem to underlie these phenomena (LPS). The last section of this review is centered on experimental approaches linking reinforcing and feeding systems with the development of alcohol abuse and dependence in the mature organism (MJL).

The explicit intention of this article is to enhance the awareness of the scientific community in general and of those directly involved in alcohol research and treatment about the need to consider alcohol within a developmental perspective. Each ontogenetic period implies specific modes of alcohol exposure and a particular sensitivity to the drug depending, among other factors, upon brain structure and metabolic capabilities (Kelly, Bonthius, & West, 1987; Spear, 2000; Spear & Molina, 2005). It is our hope that the following sections reveal the importance of differential ontogenetic experiences for the establishment or modulation of alcohol use and abuse.

ALCOHOL RESPONSIVENESS AS A FUNCTION OF FETAL EXPERIENCES WITH THE DRUG

FAS and FASD still represent the most common congenital causes of neurobehavioral alterations, including mental retardation (Riley & McGee, 2005; U.S. Department of Health and Human Services, 2000). During the last few years epidemiological studies indicate that prenatal exposure to alcohol is also a predictor of alcohol abuse later in life (Alati et al., 2006; Baer, Barr, Bookstein, Sampson, & Streissguth, 1998; Baer, Sampson, Barr, Conner, & Streissguth, 2003; Yates, Cadoret, Throughton, Stewart, & Giunta, 1998). The association between these factors is still significant when controlling for confounding factors known to affect alcohol-drinking patterns (e.g., genetic predisposition and prenatal co-use of other psychotropic agents). Different experimental approaches based on animal models, have provided useful information concerning fetal sensory and learning capabilities that can potentially help explain the strength of this association and potential mechanisms behind it.

Substantial neuroethological research shows that near term fetuses of different species (rabbits, sheep, rats, and humans; Robinson & Smotherman, 1995; Schaal, Hummel, & Soussignan, 2004; Schaal, Soussignan, & Marlier, 2002) detect and discriminate chemosensory information present in the amniotic fluid. Nonassociative (habituation) and associative learning processes determined by close temporal contiguity between chemosensory cues and biologically relevant stimuli (e.g., illness inducing agents such as lithium chloride, tactile behavioral activating stimuli, and even milk) are also found in the unborn rat (Grues, Richer, & Hars, 2004; Molina and Chotro, 1991; Petrov, Varlinskaya, & Smotherman, 2000; Smotherman & Robinson, 1985). This knowledge coupled with a growing body of evidence indicating that soon after birth the rat acquires olfactory and taste information about alcohol and associates these cues with motivational consequences of the state of intoxication (Molina, Dominguez, Lopez, Pepino, & Faas, 1999; Spear & Molina, 2005), stimulated the idea of examining fetal learning mediated by alcohol exposure.

It was first observed that even a brief (10 min) exposure to alcohol resulting from direct administration of the drug into the amniotic fluid prior to cesarean delivery (peak alcohol concentration: 100 mg%) was sufficient to establish alcohol related memories (Molina, Chotro, & Dominguez, 1995). The experimental procedure explicitly precluded fetal alcohol intoxication despite exposure to the drug's chemosensory attributes. The expression of these memories was observed through different assessments. There were neonatal variations in behavioral and autonomic responses to alcohol odor without generalization to other odorants and pups also exhibited heightened alcohol ingestion and olfactory preferences (Chotro & Molina, 1990, 1992; Domínguez, Lopez, & Molina, 1998). This brief experience with alcohol in the womb also facilitated infantile appetitive Pavlovian conditioning when using alcohol odor as a conditioned stimulus (CS) (Chotro, Cordoba, & Molina, 1991). As a whole these results indicated that brief fetal familiarization with alcohol's sensory cues promotes later behavioral affinity for alcohol. But what should be expected when fetal alcohol experiences are derived from maternal alcohol intoxication, a circumstance that implies accumulation of alcohol in the amniotic fluid as well as postabsorptive effects of the drug? Would maternal–

fetal intoxication affect fetal sensory processing and retention capabilities? Is it possible that alcohol intoxication acts as an unconditioned stimulus (US) capable of mediating associative learning that also comprises the drug's chemosensory cues? It is necessary to note that ethanol intoxication, depending on factors such as dose and postadministration time, can exert positive and negative (antianxiety) reinforcing effects or even aversive consequences (e.g., see Cunningham, Niehus, & Noble, 1993; Molina, Ponce, Truxell, & Spear, 2006; Pautassi, Sanders, Miller, Spear, & Molina, 2006). These postabsorptive motivational consequences are capable of determining the hedonic value of stimuli associated with the drug.

To answer these questions, studies were conducted where pregnant rats were intragastrically administered low to moderate doses of alcohol, yielding equivalent levels of alcohol in amniotic fluid and fetal and maternal blood (range: 40–120 mg%). This treatment was conducted during late gestation (gestational days 17–20). Neither placental or umbilical cord sizes and weights, fetal weights or gross morphological parameters of different central nervous system structures were affected by prenatal treatment. Nevertheless, alcohol experience in utero had a significant effect upon subsequent responsiveness to the drug. Neonates exposed to the drug exhibited behavioral signs indicative of alcohol odor recognition and were observed to react to the smell of alcohol in the way alcohol-naïve pups react to the smell of their own amniotic fluid (Chotro & Spear, 1997; Domínguez, Lopez, Chotro, & Molina, 1996; Molina et al., 1999). Later in life, pups subjected to intrauterine alcohol experiences showed heightened ingestion of alcohol and of a sucrose-quinine compound, which represents a psychophysical equivalent of alcohol in the rat (Domínguez et al., 1998; also see Chotro & Arias, 2003). Taste reactivity tests indicated that palatability of ethanol is enhanced in these pups (Arias & Chotro, 2005). Were these effects solely determined by sensory familiarization with alcohol? Can we completely discard associative fetal learning based on the contingency between alcohol's sensory (CS) and toxic (US) properties?

To analyze the later possibility studies were conducted using a nonalcohol CS (cineole) that could be administered to the mother and traced through chromatography. Pharmacokinetic profiles for cineole and alcohol in the amniotic fluid and in fetal–maternal blood allowed examination of whether olfactory conditioned responses were established when alcohol intoxication served as a US (Abate, Pepino, Dominguez, Spear, & Molina, 2000). With this experimental approach the contingency between the CS and alcohol's pharmacological effects could be varied in terms of temporal contiguity. Pups prenatally exposed to paired experiences between cineole and the onset of alcohol intoxication, exhibited patterns of orofacial responses (mouthing) elicited by the CS that were significantly different from those found in infants that had originally experienced the CS and the US separated by a significant time delay (4 hr) or pups born to water treated females (Abate et al., 2000; Abate, Spear, & Molina, 2001). Using a similar experimental strategy it was also observed that neonates prenatally exposed to cineole associated with alcohol intoxication show heightened responsiveness to a nutritive surrogate nipple in the presence of the odor employed as a CS during late gestation (Abate, Varlinskaya, Cheslock, Spear, & Molina, 2002).

The possibility that the consequences of intrauterine alcohol experiences are dependent not only on the drug's sensory properties but also on its unconditioned effects is further supported by the following experimental outcomes. The magnitude of certain physiological disruptions (e.g., maternal hypothermia) caused by alcohol during late gestation predicts the magnitude of behavioral orienting responses to alcohol odor in the newborn rat. This correlation is absent when hypothermia is generated by a nonalcohol stimulus (cold vehicle) or when neonatal assessments are conducted with alternative olfactory cues (Abate, Pepino, Spear, & Molina, 2004). In addition, it has recently been observed that late gestational exposure to alcohol results in postnatal sensitization to alcohol's positive reinforcing effects (Nizhnikov, Molina, Varlinskaya & Spear, 2006; also see next section of this review).

Methodological and mainly ethical considerations limit the possibility of studying these phenomena in humans. Yet, we have recently learned that moderate consumption of alcohol during human pregnancy is also strongly associated with heightened neonatal responsiveness to the odor of alcohol. In these babies, none of which presented prototypic signs of FAS, the behavioral disposition to immediately react to the presence of alcohol odor was not observed when employing alternative olfactory cues (Faas et al., 2000).

As mentioned previously, there is now considerable agreement that alcohol ingestion during pregnancy represents a risk factor in terms of later alcohol-related problems. Deleterious actions of alcohol in the embryo and the fetus include alterations in neurochemical systems (e.g., GABA, dopamine; endogenous opioids) and neuroendocrinological processes (stress-related reactivity mediated by the HPA axis) known to modulate behavioral affinity for alcohol (for reviews see Chotro, Arias, & Laviola, 2006; Spear & Molina, 2005). Beyond these effects, it seems necessary to consider that intrauterine exposure to alcohol can also trigger fetal sensory and learning capabilities about alcohol, even when the level of exposure is well below that for which teratogenic effects have currently been documented. This adds yet another reason to prevent maternal alcohol intake during pregnancy.

EARLY ONTOGENY OF ALCOHOL INTAKE AND REINFORCEMENT

The preceding section reminds us of two similar facts: (1) humans exposed prenatally to alcohol are at risk for excessive alcohol intake and alcohol abuse; (2) elevated alcohol ingestion occurs later in life among rats exposed to alcohol prenatally or during the first two postnatal weeks. In terms of neuroanatomy (Bayer, Altman, Russo, & Zhang, 1993; Dobbing & Sands, 1979) the latter period can be viewed as comparable to the third trimester human fetus and neonate and has been applied effectively as an animal model for understanding brain damage in humans exposed prenatally to large amounts of alcohol (Chen & West, 1999; Goodlett & Johnson, 1999). Throughout this and subsequent periods of infancy (P0–P21) we have sought to describe and understand the ontogeny of alcohol ingestion and, separately, alcohol reinforcement [which has been functionally dissociated from ingestion (Czachowsky, Legg, & Stansfield, 2006; Files, Denning, Hyttia, Kiianmaa, & Samson, 1997; Files, Denning, & Samson, 1998; Samson & Hodge, 1996)]. How alcohol ingestion and reinforcement are controlled neurally and physiologically during infancy, how they change ontogenetically and through what mechanisms, should help reveal how alcohol interacts with the developing human brain and help foster techniques for therapy or prevention of alcohol-related brain damage.

How does the rat respond to alcohol during early ontogeny? The short answer is, they ingest it more readily than older animals and find it quite reinforcing. A more complete answer has been possible due in large part to techniques developed by developmental psychobiologists in the study of the ontogeny of ingestion and the ontogeny of learning (e.g., Hall, 1990; Robinson, Arnold, Spear, & Smotherman, 1993; Robinson & Smotherman, 1995). Given the adult rat's well-known rejection of alcohol in concentrations above 5 or 6% and at most grudging tolerance of lower concentrations, it was surprising to discover the infant's high level of alcohol ingestion at these and higher concentrations. In one of our first published tests of this effect it was clear that infant rats not only readily ingest 15% alcohol but also ingest more 15% alcohol than water (Lee, Crawford, & Spear, 1998). This effect—greater intake of alcohol than water—has been found in many subsequent experiments to emerge at about P6–8.

Newborn rats 3 hr after birth drink (through an artificial nipple) more than twice as much 5% alcohol as water, as much 5% alcohol as 0.1% saccharin or milk, and about 0.5–0.6 g/kg of absolute alcohol during a 10-min period when alcohol concentration is either 5% or 10%, doses shown to have appetitive reinforcement effects (Petrov, Varlinskaya, & Spear, 2001). In circumstances characterized by Hall (1990) as “independent feeding”—consumption off the

floor (COF) or from intraoral infusion—older pups consume similarly remarkable amounts of alcohol. When allowed to drink 10–25% alcohol every other day beginning at P2, intake of alcohol increases strikingly, and by P10 and P12 roughly 4 g/kg of 25% alcohol is ingested within a 20-min period (Sanders & Spear, in press). During this same period (P2–P12) relatively little water (0% alcohol) is ingested and the amount increases little if at all with ontogeny. At P12 and P18, pups ingest enough 30% v/v alcohol to bring their BECs to nearly 300 mg/dl (Truxell & Spear, 2004). Although with this mode of ingestion some of the alcohol in blood (20–40 mg/dl) can be due to inhalation or to transdermal absorption, high levels of alcohol are ingested and high BECs achieved even when intake is by intraoral infusion, a common test of infant ingestion with which such inhalation and transdermal absorption are negligible (Truxell and Spear). So without any initiation whatsoever, and without taking measures to increase its palatability, infant rats readily consume huge amounts of alcohol within a short period. When mode of intake is COF at all ages and concentration of alcohol is moderate (15%), it begins to decline after about P12, declines further into the juvenile period (P21–27) and still further through adolescence (P28–42) before reaching its low point in adulthood (Truxell, Molina, & Spear, in press).

An appetitive reinforcement effect of alcohol was established in the neonate with several experiments (e.g., Cheslock et al., 2001). Was this effect due only to alcohol's flavor and calories? To answer this question we have presented alcohol as an US through routes that bypass the mouth and stomach. With intraperitoneal injection of alcohol as the US paired with a CS consisting of suckling on a nipple for water (which has no reinforcing effects in infant rats) we found in several experiments that doses of .125, .25 and, to some extent, .5 g/kg provided significant reinforcement effects (Nizhnikov et al., 2006; Petrov, Varlinskaya, & Spear, 2003). We were aware that hematogenic sources of gustatory or olfactory stimulation are possible even with i.p. administration, so we sought to further reduce or eliminate alcohol's taste and caloric properties by central injection of alcohol into the cisterna magnum. We previously had used intracisternal injection at this age to reveal reinforcing effects of the endogenous kappa opioid receptor agonist, dynorphin A(1,13) (Petrov, Nizhnikov, Varlinskaya & Spear, 2006).

Blood alcohol concentrations (BAC) of 15–35 mg% yielded reinforcing effects with alcohol delivered either intraorally or intraperitoneally, providing a rough guide as to the range of doses to test with central injection of alcohol. Intracisternal alcohol was appetitively reinforcing over a wide range of doses (25–200 mg%). The conclusion is that although the flavor and caloric content of alcohol might conceivably contribute to alcohol reinforcement in newborn rats (3-hr old), the contribution is quite small in view of the strong alcohol reinforcement found at comparable BACs in the absence of alcohol's flavor and caloric properties.

Appetitive reinforcement from alcohol has not been clear in infant (preweanling) rats tested with primary Pavlovian or operant conditioning procedures. We have, however, begun to observe such effects with second-order conditioning procedures (Molina et al., 2006; Molina, Pautassi, Truxell, & Spear, in press). With these tests alcohol intoxication 5–10 min after 0.5 g/kg or 30–40 min after the same dose have shown to have appetitive reinforcement value. Intoxication by 2 g/kg also yielded appetitive reinforcement 5–10 min after its intubation, but 30–40 min after intubation of 2 g/kg the result was conditioned aversion, indicating biphasic motivational effects of alcohol.

Finally, we have begun to consider brain mechanisms responsible for alcohol reinforcement early in life. Our first candidates have been the opioid system and alcohol metabolism in the brain. In several experiments with neonates, Nizhnikov et al. (2006) found that alcohol reinforcement was reduced drastically by pharmacological blockade of either kappa or mu receptors, implying the importance of these opioid receptors for alcohol reinforcement. We

have also found that catalase, which acts in the brain to convert alcohol to acetaldehyde, contributes to the reinforcing effects of alcohol in neonates. Catalase levels in the brain are high soon after birth and then decline in a manner similar to that of alcohol intake. The infant rat has very little alcohol dehydrogenase in the liver, so catalase is apparently the primary enzyme for the first step of alcohol metabolism in early ages, certainly in the brain (Del Maestro & McDonald, 1987). Nizhnikov et al. (in preparation) have found that inhibition of catalase activity in the brain decreases drastically the reinforcing effects of centrally administered alcohol, implying that subsequent products of metabolized alcohol may be the primary source of appetitive reinforcement rather than alcohol itself. Ontogenetic changes in catalase activity, along with those of specific receptor activity in the opioid and other neurotransmitter systems, may help determine age-related differences in alcohol intake and reinforcement.

EARLY LEARNING ABOUT THE SENSORY PROPERTIES OF ALCOHOL

First experiences with flavors occur prenatally in amniotic fluid and then continue when infants experience the flavors of the foods consumed by their mothers in breastmilk. These chemosensory experiences provide a sensory bridge for fetal and neonatal niches (Mennella, Jagnow, & Beauchamp, 2001; Spear & Molina, 2005; Schaal et al., 2004) that may confer survival advantages during weaning since infants acquire information about the dietary choices of their mothers (Mennella et al., 2001; Nolte, Provenza, & Balph, 1990). Teleologically, one can argue that it is important for infants to accept and be particularly attracted to the flavors consumed by their mothers since these are the flavors that are associated with safe and nutritious foods, or at the very least, foods mothers have access to, and hence the foods to which they will have the earliest exposure. But in addition to being a vehicle for orosensory learning about maternal dietary choices, amniotic fluid and mothers' milk provide sensory information about other choices of the mother, namely, the flavors of tobacco and drugs such as ethanol (Mennella & Beauchamp, 1991, 1998b).

It is of interest to note that in the not-so-distant past, alcohol use during pregnancy and lactation was declared "safe" by leading experts (see Golden, 2005; Mennella, 1999). More than being deemed safe, the lore of many cultures relayed that alcohol could optimize the process of lactation since drinking small quantities of alcohol shortly before nursing was believed to increase milk yield, facilitate milk let-down, and relax both mothers and infants (Mennella). Scientific research conducted during the past several decades calls these practices and this lore into serious question, however. Not only has the teratogenicity of ethanol been well-documented during the past decades in clinical cases as well as animal models, its use during lactation, which is the focus hereafter, disrupts lactational performance and alters infant behavior and development ((Little, Anderson, Ervin, Worthington-Roberts, & Clarren, 1989).

Contrary to popular beliefs, infants actually ingest less milk at the breast during the hours immediately following maternal alcohol consumption (Mennella & Beauchamp, 1991, 1993). This diminished intake was not due to the infants rejecting the flavor of alcohol in milk (Mennella, 1997). Rather, it was due to alcohol-induced decreases in milk production (Mennella, 2001) and disruption in the key hormones underlying lactational performance (Mennella, Pepino, & Teff, 2005). The diminished oxytocin response was significantly related to decreases in milk yield and milk ejection, thus suggesting that the alcohol-induced reductions in oxytocin mediate the diminished milk production by lactating women and disruption in infant feeding. Based on this science, it would seem that the recommendation for lactating women to drink a glass of beer or wine shortly before nursing may actually be counterproductive. While mothers may be more relaxed after a drink, their babies will ingest less milk (Mennella and Beauchamp) and infants' sleep will be disrupted in the short term (Mennella & Garcia-Gomez, 2001).

Beyond alcohol's teratogenic effects on the fetus and disruptive effects on the lactational process, a growing body of experimental research in animal models suggests that during ethanol exposure, the fetus or young infant can acquire an association between ethanol's orosensory properties and pharmacological consequences, causing the animal subsequently to seek out ethanol (Molina et al., 2006; Pepino, Abate, Spear, & Molina, 2002). Moreover, young animals learn to associate the odor of ethanol within the context of the mother and the effects that alcohol has on her behaviors (Molina, Pepino, Johnson, & Spear, 2000). To study whether early exposure to the odor of ethanol in the context of maternal drinking could alter responsiveness to alcohol in humans, one is limited and has to employ a correlational rather than experimental approach. Nevertheless, recent experimental studies in humans are quite consistent with animal model findings and together they suggest that pre- and postnatal experiences with odors and flavors, including ethanol, bias the infants' behaviors and preferences during infancy and childhood.

Newborns can discriminate full-strength homologous alcohols on the basis of odor alone (Rovee, 1972) and can retain olfactory information when ethanol is experienced in amniotic fluid (Faas et al., 2000) and mother's milk (Mennella, 1997). Moreover, when breast-fed infants were tested with toys that were identical in appearance but differed in their characteristic scent, infants who had more exposure to ethanol as inferred from parental drinking habits, behaved differently in the presence of an ethanol-scented toy when compared with less exposed infants (Mennella & Beauchamp, 1998a). Of the four behaviors monitored in the study (mouthing, looking, manipulating the toy, and vocalizing), this differential response was manifested in mouthing the ethanol-scented toy more. This learning appeared to be keenly selective since the response was specific to the ethanol odor and not other closely related aromas.

That early experiences can also result in the generation of aversive memories about alcohol was evident in a study on older aged children (Mennella & Garcia, 2000). Here 3- to 6-year-old children's hedonic response to the odor of alcohol was related to the emotional context in which mothers experience alcohol. That is, children whose parents drank alcohol to change their state of mind or reduce dysphoric feelings were significantly more likely to judge the odor of beer as unpleasant when compared to similarly aged children whose parents did not drink to escape. This difference between the groups was specific to the odor of alcohol.

In conclusion, research in both humans and animal models suggests that at least some of the early learning about alcohol is based on sensory experiences and clearly anchor it to the frequency and the emotional context in which their parents experience alcohol. Memories evoked by odors are more emotionally charged than those evoked by other sensory stimuli (Herz & Cupchik, 1995) possibly due to direct connections between the olfactory and limbic systems (Cahill, Babinsky, Markowitsch, & McGaugh, 1995), the latter of which is necessary for the expression and experience of emotion (Aggleton & Mishkin, 1986). Like children whose parents drink to escape from their dysphoric mood, children whose mothers smoke to reduce mood disturbance may be learning that their parents tend to smoke during negative rather than positive social situations. Whether the emotional response to the scent of alcohol (or tobacco; Forestell & Mennella, 2005) conditioned during early childhood persists or can explain behaviors during adolescence (see Varlinskaya and Spear, 2006a) and beyond is an important area for future research.

ADOLESCENCE: DIFFERENTIAL ALCOHOL SENSITIVITIES AND INTAKE

Adolescence, defined as the transition between immaturity and maturity, is a stage of development characterized by dramatic alterations in physiology and behavior. Notable among the physiological changes of adolescence are the hormonal and physiological transformations associated with puberty that ultimately lead to sexual maturation and the emergence of

secondary sexual characteristics (e.g., Graber & Brooks-Gunn, 1998). Adolescence is also associated with a major growth spurt that is associated in part with elevated release of growth hormone as well as often notable increases in food intake (Post & Kemper, 1993). At least as dramatic as these transformations in body appearance are the marked physiological transformations that occur within the brain of the adolescent, along with the emergence of a variety of adolescent-typical behaviors that include increases in peer-directed social interactions (LaGreca, Prinstein, & Fetter, 2001) and elevated novelty-seeking and risk-taking (Irwin, 1989; Trimpop, Kerr, & Kirkcaldy, 1999). Interestingly, similar physiological transitions and adolescent-typical behavioral characteristics are evident among adolescents across a variety of mammalian species, findings consistent with the notion that adolescence has been a highly conserved developmental stage during the process of evolution (Savin-Williams & Weisfeld, 1989), and leading credence to the utility of animal models to study certain aspects of adolescence (see Spear, 2000, for review).

Many of the changes occurring during the adolescent sculpting of brain involve the culling of synaptic connections, with a decline of close to one-half of the average number of synapses in some brain regions (Rakic, Bourgeois, & Goldman-Rakic, 1994), along with the formation of some new connections. Particularly pronounced culling occurs within glutaminergic systems providing excitatory input to neocortex (Bourgeois, Goldman-Rakic, & Rakic, 1994). This waning of excitatory drive is thought to contribute to the decline in brain energy utilization seen during adolescence that serves to transform the immature, high-energy-demanding juvenile brain into the more energy-efficient brain of the adult (e.g., Chugani, 1996).

Although adolescent-associated changes are seen throughout the brain across a variety of mammalian species, regions undergoing particularly pronounced transformation include the mesocorticolimbic dopamine system and associated terminal regions (e.g., prefrontal cortex, nucleus accumbens, hippocampus, amygdala) (e.g., Andersen, Dumont, & Teicher, 1997; Cunningham, Bhattacharyya, & Benes, 2002; Kellogg, Awatrami, & Piekut, 1998; Rakic et al., 1994; Teicher et al., 1993). These regions form part of the so-called brain “reward circuitry” thought to be critical for labeling both natural stimuli (including food, social stimuli, novelty) and “nonnatural” rewards (such as alcohol and other drugs) with reward significance, incentive salience, and emotional value (Le Moal & Simon, 1991; Robinson & Berridge, 2003). Normal developmental changes in these brain regions during adolescence are thus positioned for modulating a number of adolescent-typical behavior patterns, including increases in peer-directed social affiliations, risk-taking, and novelty seeking. These and other brain regions undergoing developmental change during adolescence are also affected by alcohol, which may alter alcohol sensitivity and adaptations during adolescence, possibly increasing propensity for adolescent alcohol use.

Consistent with the notion that adolescent alcohol use may be in part biologically based, higher levels of per episode alcohol intake are seen during adolescence than in adulthood. This phenomenon is not only observed in human adolescents (SAMHSA, 2004), but also among adolescents of other species as well. For instance, under a number of circumstances, adolescent rats voluntarily drink 2–3 times more sweetened alcohol in their home cage than do adults (Brunell & Spear, 2005; Doremus, Brunell, Rajendran, & Spear, 2005), effects that are neither related to the sweetener per se nor to the caloric content of the alcohol (Doremus et al.). Animal studies have shown that the elevated alcohol consumption of adolescents may be related in part to their resistance to many of the acute intoxicating effects of alcohol that are presumed to serve as cues to limit intake. Effects of alcohol for which adolescents are relatively insensitive include alcohol-induced motor impairment (e.g., Silveri & Spear, 2001; White, Bae, et al., 2002; White, Truesdale, et al., 2002), social impairment (Varlinskaya & Spear, 2002), dysphoria (Varlinskaya, Falkowitz, & Spear, 2006), and sedation (e.g., Moy, Duncan, Knapp, & Breese, 1998; Silveri & Spear, 1998). These adolescent-typical insensitivities to alcohol are

not related simply to pharmacokinetic factors (see Spear, 2007, for further discussion), but instead may reflect, at least in part, the more rapid development of acute tolerance in immature animals relative to their adult counterparts (Silveri & Spear, 1998; Varlinskaya and Spear, 2006a).

Whereas adolescents show an attenuated sensitivity to many alcohol effects, they show a greater sensitivity to a few restricted effects of alcohol, including alcohol-induced impairments in hippocampal LTP (Pyapali, Turner, Wilson, & Swartzwelder, 1999; Swartzwelder, Wilson, & Tayyeb, 1995) and alcohol-related memory disruptions (Markwiese, Acheson, Levin, Wilson, & Swartzwelder, 1998). Adolescent rats also have been shown to be considerably more sensitive than their adult counterparts to alcohol-induced social facilitation, with adolescents showing increases in social interactions following challenge with low doses of alcohol in familiar (low anxiety producing) situations, social facilitation that is not evident in adults (Varlinskaya & Spear, 2002).

These differing ontogenetic patterns of alcohol sensitivities and insensitivities may be related in part to differential rates of maturation of the many neural systems that have been shown to contribute to various alcohol effects. For instance, developmentally enhanced NMDA receptor expression has been related to the unusually potent alcohol-induced disruption of neural plasticity among adolescents (e.g., Li, Wilson, & Swartzwelder, 2002; Pyapali et al., 1999; Swartzwelder et al., 1995), whereas mu opiate receptors have been found to contribute to the alcohol-related enhancement of social interactions among adolescents (Varlinskaya and Spear, 2006b). In contrast, there is evidence that the attenuated sensitivity of young animals to alcohol's sedating effects is related in part to developmental immaturity in GABA_A receptor systems (Moy et al., 1998; Silveri & Spear, 2002).

By necessity, research exploring sensitivity to alcohol during adolescence has largely been restricted to investigations using animal models, given ethical constraints against giving alcohol to youth under the legal drinking age. Nevertheless, although relevant data are rare, there are a few intriguing hints that human adolescents likewise may differ from adults in their sensitivity to alcohol in ways reminiscent of the animal data. In terms of alcohol-related memory disruptions, late adolescent (21- to 24-year-old) college students were found to be more sensitive to alcohol than individuals several years their senior (25- to 29-year-old; Acheson, Stein, & Swartzwelder, 1998). Similarly, although no studies have directly compared human adolescents and adults in terms of alcohol-induced social facilitation, survey studies have revealed that adolescents drink primarily for social facilitation (e.g., Berkowitz & Perkins, 1986; see also Beck, Thombs, & Summons, 1993). Finally, reminiscent of studies reporting an attenuation in the intoxicating effects of alcohol among adolescents when using animal models, evidence for an attenuated sensitivity to alcohol's intoxicating effects was likewise found in human adolescents in a study by Behar et al. (1983). In this older study, 8- to 15-year-old boys were given a dose of alcohol sufficient to induce blood alcohol levels (34–35 mg%) in the range viewed as intoxicating in adults (20–90 mg%—see Eckardt et al., 1998). These researchers were “impressed by how little gross behavioral change occurred in the children... after a dose...intoxicating in an adult population” (Behar et al., p. 407), noting that among these boys “none behaved grossly ‘intoxicated’ as our adult...subjects were” (p. 408).

Relative sensitivity to alcohol is important, given that an insensitivity to the intoxicating effects of alcohol predicts later problematic involvement with ethanol and is characteristic of individuals at genetic risk for alcoholism (Schuckit, 1994). Moreover, the insensitivity to alcohol seen normally during adolescence may be further attenuated by a history of repeated use, given initial reports that adolescents develop tolerance to alcohol at least as rapidly as do adults (e.g., Varlinskaya & Spear, 2007). Thus, when individuals at genetic risk reach adolescence and begin to drink repeatedly, this combination of alcohol insensitivities may

combine to promote particularly high intake levels, increasing their vulnerability to alcohol-induced disruptions in brain plasticity and memory, and perhaps placing them on a trajectory for the emergence of later alcohol use disorders and dependence.

DEVELOPMENT OF ALCOHOL DEPENDENCE: THE ROLE OF FEEDING, NUTRITION, AND REINFORCEMENT SYSTEMS

Consumption of alcoholic beverages is often associated with the best of times (e.g., a champagne toast at a wedding) and also the worst of times (e.g., the loss of health, social relations, and employment with alcoholism). Complicating our understanding of the pharmacological, behavioral, and clinical aspects of alcohol use, abuse, and dependence is that ethanol is both a food as well as a drug. This added dimension may contribute to alcohol abuse and dependence as nutritional systems deteriorate with chronic ethanol intake. Moreover, alcohol produces a variety of behavioral effects including mild euphoria and elation, stimulation, anxiolytic effects, sedation, analgesia, and increased appetite. Understanding the neurobiological basis of these effects has been most difficult (see Lewis, 1996). This quest has been made more difficult by another unique feature of alcohol: unlike other drugs of abuse, it has no specific receptor.

Several of the behavioral effects may be the basis of alcohol reinforcement. Like other drugs of abuse, it is self-administered and elicits similar response characteristics in animal models of abuse. Oral self-administration can be established in rats by training them to initially drink low alcohol concentrations and gradually increasing concentration until animals consume significant concentration of the drug (e.g., 10% or more). This can be accomplished without enhancing the taste with sucrose or saccharin, which complicates the analysis of the basis of alcohol reinforcement by adding additional reinforcing substances. The effects of the combination of alcohol with sweet tastes on acquisition and maintenance of the self-administration are to a large extent unknown. Using a two bottle choice between alcohol solutions and water, Lewis and coworkers (Martinetti, Andrzejewski, Hineline, & Lewis, 2000; Martinetti, Khan, & Lewis, in press) have shown that alcohol exhibits choice and consumption characteristics of other reinforcers.

In addition to oral self-administration, alcohol can enhance electrical brain stimulation reward (BSR) when tested during the ascending limb of the blood alcohol curve (BAC), similar to other drugs of abuse (Lewis & June, 1990). These effects are found with low doses when testing occurs soon after parenteral administration or with oral self-administration (which prolongs the rise in BAC) (Bain & Kornetsky, 1989). Therefore alcohol, like other drugs of abuse, has rewarding effects, although they are apparently not as robust as cocaine and opioids.

Alcohol has also been shown to produce enhanced performance in anti-conflict paradigms such as the elevated plus maze (Lister, 1988). Performance in these tasks is indicative of the anxiolytic properties of alcohol. Although weak in comparison to benzodiazepine anxiolytics; they may be an important dimension of alcohol in the development of abuse. Therefore, alcohol has both negative as well as positive reinforcing or rewarding effects that could contribute to the acquisition of abuse and development of dependence.

The neurobiological data suggest the role of several neurochemical systems in these reinforcement effects. Measurement of functional brain activity using 2-deoxyglucose autoradiography after alcohol administration suggests increased activity in the ventral striatum (Lewis & June, 1990; Lewis, Perry, June, Garnett, & Porrino, 1990; Williams-Henby & Porrino, 1994). These effects include increased release of dopamine (DA) (Rada, Johnson, Lewis, & Hoebel, 2004). This increase is consistent with data on other drugs of abuse producing similar effects on DA (DiChiara, 1995; Wise & Bozarth, 1987). The role of GABA-benzodiazepine

(GABA-BZD) receptors has also been implicated in alcohol reinforcement (June et al., 2006; Susdak et al., 1986). Inverse BDZ agonist such as RO 15-4513 and more specific compounds (June et al.) have been shown to block alcohol anti-conflict effects, oral self-administration, and ataxia. Although these data suggest a major role of DA and GABA-BZD in alcohol reinforcement, other neurochemical systems also contribute to these effects. However, a review of this research is beyond the scope of this article.

As previously mentioned, alcohol is both a food as well as a drug of abuse. It is rich in calories, containing 7 kcal/g (fats = 9, carbohydrate = 3.75, and proteins = 4). The interrelationship of alcohol with food intake is quite substantial. Food deprivation increases alcohol consumption in rats (Carroll & Meisch, 1984) and alcohol consumption increases food intake in humans (Caton, Ball, Ahern, & Hetherington, 2004; Caton, Marks, & Hetherington, 2005). Concerning the latter, there are alcoholic beverages that are categorized as aperitif, a stimulant to appetite. Moreover, the strategy of restaurant staff of filling your beverage order before taking your food order is no accident of protocol and is everyday confirmation of the enhancement phenomenon.

As alcohol dependence develops, there is an increase in alcohol-derived calories and a concomitant decline in many organ systems. These concomitant effects are most evident in the severely dependent alcoholic. Liver, kidneys, pancreas, and other gastrointestinal organs show increasing symptoms of pathology leading to compromised absorption and distribution of nutrients (Lieber, 1988). Moreover, brain systems such as cognitive and motor functions are also adversely affected. It is, therefore, conceivable that brain systems that control food intake and monitor the message of nutritional status from peripheral organ systems may also be adversely affected. This logic led to recent interest in examining the role of brain feeding mechanisms in the development of alcohol dependence.

There are 27 or more neuropeptides that either increase or decrease food intake. One of these found in high concentration in hypothalamic sites is galanin. Microinjection of galanin in the hypothalamus increases food intake, especially fat-rich foods (Kyrkouli, Stanley, & Leibowitz, 1986) and also increases DA in the nucleus accumbens (Rada, Mark, & Hoebel, 1998). Moreover, fat-rich diets increase galanin expression in the hypothalamus (Leibowitz, Akabayashi, & Wang, 1998). Based on these data, Lewis, Johnson, Waldmen, Leibowitz, & Hoebel (2004) investigated the role of galanin on alcohol intake. They found that in rats trained to prefer alcohol over water for many weeks, microinjection of this 29-30 amino acid peptide into the third ventricle near the paraventricular nucleus (PVN) (Lewis et al.) or in the nucleus itself (Rada, Avena, Leibowitz, & Hoebel, 2004) increased alcohol intake. Furthermore, it has been recently observed that administration of alcohol increases galanin expression in the hypothalamus (Chang et al., 2007). In rats that had been consuming alcohol for 6 or more weeks, galanin did not increase the consumption of their chow diet. These data suggest a possible role in galanin in alcohol consumption and possibly in the development of alcohol dependence.

A theory that embraces this idea might be as follows: chronic alcohol consumption may change the normal role of galanin in motivating the consumption of fat-rich foods to motivating the consumption of alcohol (Lewis et al., 2005). As with the positive feedback mechanism found with galanin and fat consumption, there may be positive feedback between galanin and alcohol consumption: alcohol increasing galanin production which then increases alcohol consumption. New clinical data indicate that galanin expression may be associated with alcohol dependence in some ethnic groups (Belfer et al., 2006).

Recent research indicates that galanin may not be the lone feeding peptide playing a role in alcohol consumption. Enkephalin and dynorphin concentrations along with galanin, were found to be increased in the PVN with injection and consumption of alcohol (Chang et al.,

2007). Like galanin, both of these endogenous opioids increase food intake. These new findings further suggest that chronic alcohol intake alters food intake mechanisms. The alteration of basic feeding mechanisms could be important in maintaining drinking in those severely dependent on alcohol, motivating their consumption perhaps more powerfully than the motivation derived from the relatively weak reward and negative reinforcement properties of alcohol in the adult organism.

SUMMARY AND FINAL CONSIDERATIONS

Beyond a teratological perspective, it seems clear that infants and even fetuses are capable of rapidly acquiring information about sensory and pharmacological attributes of alcohol. Prenatal, neonatal, and infantile exposure to even low to moderate alcohol doses set the opportunity for processing these attributes, to establish associations between them or even to acquire memories related with the emotional context that surrounds the original contact with alcohol (see “Introduction,” “Alcohol Responsiveness as a Function of Fetal Experiences With the Drug,” and “Early Ontogeny of Alcohol Intake and Reinforcement” in the present review). Both the animal and human literature indicate that these early experiences can exert short- and long-term effects upon subsequent alcohol responsiveness in terms of facilitating later recognition, discrimination, and even acceptance of the drug’s chemosensory properties. These early experiences also reveal high predisposition for alcohol ingestion and a marked sensitivity to the positive reinforcing effects of the drug; phenomena that seem to be regulated by different mechanisms (see Files, Denning, Hyttia, Kiianmaa, & Samson, 1997; Samson, Files, Denning, & Marvin, 1998). While heightened affinity for alcohol ingestion and marked sensitivity to alcohol’s reinforcing effects are often found early in ontogeny, similar findings are less frequent in the mature organism, particularly when studying genetically heterozygous animals (i.e., neither genetically selected for the predisposition to ingest high levels of the drug without initiation procedures nor for their sensitivity to alcohol reinforcement; e.g., see McBride & Li, 1998; see “Introduction,” “Alcohol Responsiveness as a Function of Fetal Experiences With the Drug,” “Early Learning About the Sensory Properties of Alcohol,” and “Adolescence: Differential Alcohol Sensitivities and Intake”).

As mentioned, adolescents relative to adults appear more likely to abuse alcohol probably because of their marked insensitivity to the drug’s motor and social impairing effects coupled with a rapid development of acute tolerance. Relative to the effects of alcohol upon social interactions, adolescents challenged with low alcohol doses are likely to exhibit behavioral signs of social facilitation (see “Early Learning About the Sensory Properties of Alcohol”). This not only alludes to possible reinforcing effects of the drug but also to possible passive social influences upon peers. In other words, affinity for alcohol cannot only be determined by what the process of intoxication affords to the individual itself; it can also be derived from the perception of the drug’s effects on socially related counterparts (in the case of humans see: Epstein, Botvin, Baker, & Diaz, 1999; Wood, Read, Palfai, & Stevenson, 2001; in rats: Fernandez-Vidal & Molina, 2004; Hunt, Holloway, & Scordalakes, 2001; Hunt, Lant, & Carroll, 2000). Similarly, to better understand the effects of alternative early alcohol experiences, such as those anchored in the context of breastfeeding, we need to consider a unit of analysis that goes beyond the individual. As discussed, alcohol-related memories derived from the nursing process are better understood when considering infantile perception of the effects of maternal intoxication, including emotional aspects linked with maternal use of the drug (see “Early Ontogeny of Alcohol Intake and Reinforcement”).

Relative to the development of alcohol dependence, it appears that neuropeptides (e.g., enkephalin, dynorphin, and galanin) involved in the regulation of feeding mechanisms play a significant role in maintaining chronic alcohol drinking. The experimental data obtained in adult rats suggest positive feedback mechanisms involving alcohol consumption and the

motivation for food intake. To the extent that these mechanisms can help explain affinity for alcohol ingestion during earlier stages of development remains an open question. The following considerations seem to support the need for earlier ontogenetic studies. The first issue relates with the fact that periadolescence is characterized by a unique rate of growth associated with the greatest caloric intake of any time in the life span (Nance, 1983;Spear, 2000). As stated, alcohol is also a food rich in calories. The interactions between alcohol intake and food regulation remain to be systematically studied during this stage in ontogeny. The second consideration relates with recent findings indicating that the endogenous opioid system involved in the control of feeding mechanisms in adults is also implicated in early appetitive early reinforcement (see “Alcohol Responsiveness as a Function of Fetal Experiences With the Drug” and “Adolescence: Differential Alcohol Sensitivities and Intake” in this review).

During the upcoming years we will likely confront, among others, new questions related with neurobiological and socio-environmental factors responsible for alcohol responsiveness across ontogeny, alcohol-related outcomes based on sequential ontogenetic experiences with the drug, and the interactions between genetic predispositions and alcohol experiences during development. We hope that the present review aids in the formulation of these questions by taking into account the multiple links existing between alcohol and developmental processes.

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