



Exposure to maternal odor enhances intake of a taste that mimicks the sensory attributes of ethanol

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Abstract

Early exposure to ethanol increases subsequent acceptance of this drug. Little attention, however, has been devoted to the interaction of the taste of the drug with other, familiar or non-familiar, odors contingent with ethanol access, particularly early in ontogeny. This study assessed the influence of exposure to maternal odor on intake and grasp responses to an artificial nipple providing a solution (a sucrose-quinine mix) that emulates the taste of alcohol, in 4-day-old rat pups. The results showed that the mother's odor enhanced intake from and seeking responses to an artificial nipple that provided the solution that mimicked the taste of alcohol (Experiment 1). This pattern of results was not evoked by the odor of an unrelated dam (Experiment 2), nor was it observed when the nipple delivered water. The main new finding of the present study is that 4-day-old rats tested in the presence of the mother (and hence exposed to her odor cues) exhibited enhanced seeking and intake of a solution that mimics the chemosensory properties of ethanol.

Keywords Odor · Taste · Ontogeny · Rats

Introduction

The roots of alcohol-use problems (i.e., alcohol abuse and dependence) can be traced to very early stages in life (Molina, Spear, Spear, Mennella, & Lewis, 2007). Human fetuses or babies can be involuntarily exposed to alcohol through different cultural practices, e.g., through breast milk or amniotic fluid, after maternal intoxication with the drug. Epidemiological and pre-clinical research indicates that these early experiences significantly modulate subsequent voluntary alcohol drinking (March, Abate, Spear, & Molina, 2009).

In the not too distant past (Mennella & Beauchamp, 1993a), it was considered that drinking small quantities of alcohol before nursing increased milk yield, facilitated milk let-down, or induced relaxation of the mother-baby dyad. Abundant evidence, however, indicates that drinking before nursing disrupts lactation performance and alters infant behavior and development (Mennella & Gerrish, 1998; Zeanah, Boris, & Larrieu, 1997). Furthermore, ethanol alters the flavor of breast milk, a change that results in an altered suckling behavior pattern. Mennella and Beauchamp (1991a; also see Mennella, 1999) observed that babies whose mothers consumed alcohol before nursing, compared to babies whose mothers had not consumed alcohol, performed more suckling during the first minute of the meal, yet they consumed significantly less milk by the end of the observation.

These studies (Mennella & Beauchamp, 1991a; Mennella, 1999) inferred that ethanol changed the flavor of the milk or induced sedation or activation. The influence of the maternal odor in the context of suckling, and the possibility of this odor promoting or coming into association with ethanol intake or exposure, has not, however, been considered.

The present study employed an animal (rat) model in which tastes and odors interact in the context of suckling for a substance (a quinine-sucrose compound) that emulates the taste of

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alcohol. Preweanling and neonate rats detect and discriminate between flavors, even when taste buds are not fully developed (Ganchrow, Steiner, & Canetto, 1986; Nizhnikov, Petrov, Varlinskaya, & Spear, 2002). In preweanling rats, familiarization with the odor of ethanol (Bannoura, Kraebel, Spear, & Spear, 1998) or with ethanol's unconditional effects (Arias & Chotro, 2005a; Diaz-Cenzano & Chotro 2010; Kiefer & Lawrence, 1988) results in (1) a greater preference for ethanol's odor and (2) a greater intake of either ethanol or a sucrose-quinine mix, which mimics the psychophysical properties of ethanol (Kiefer, Bice, Orr, & Dopp, 1990; López & Molina, 1999).

Olfactory stimuli are critical during the early stages of life in the development of mammals. Altricial species learn behaviors that facilitate approach towards the caregiver (Moriceau & Sullivan 2005). The maternal odor changes depending on diet, and rat pups are born without fully developed visual and auditory systems. Such flexibility in odor learning allows pups to find the nest and maternal nipple through smell (Pedersen, Williams, & Blass, 1982). This species exhibits a sensitive period, which lasts about 10 days from the time of birth, in which odor pre-exposure results in long-lasting learned preferences (Moriceau, Roth, Okotoghaide, & Sullivan, 2004; Upton & Sullivan, 2010). Such olfactory learning continues repeatedly throughout the early postnatal period, which presumably allows the infant to adjust to changes in the mother's odor (Landers & Sullivan, 2012). The relevance of this age-specific predisposition declines as subjects undergo transition into adolescence and adulthood. Previous data from our lab indicated that stimulation with a familiar, pre-exposed odor (i.e., lemon scent) either during gestational or postnatal life, increased seeking and intake of quinine (an aversive solution; Berridge, 2000) in neonate rats tested via an artificial nipple (Kamenetzky, Suárez, Pautassi, Mustaca, & Nizhnikov, 2015; Kamenetzky, Suárez, Ifran, Nizhnikov, & Pautassi, 2018). Furthermore, other studies from our laboratory showed that the presence of maternal odor also increased these ingestive behaviors toward a surrogate nipple at postnatal day (PD) 4 (Ifran, Suárez, Pautassi, & Kamenetzky, 2018). This suggested that familiar odors can switch the hedonic value of aversive solutions in rats, and reproduced results of greater acceptance of unpalatable flavors seen in studies with human babies. During the first 4 months of life, human infants exhibit a sensitive period in flavor programming, characterized by an enhanced predisposition to accept unpalatable flavors. Protein hydrolysate formulas (which are bitter and have a rancid smell) are accepted before 4 months of age, yet strongly rejected by older infants and children (Beauchamp & Mennella, 2011; Mennella & Beauchamp, 1996). The mechanisms of this flavor programming in infancy and the action of both senses (smell and taste)

working jointly during early ontogeny have not been widely explored.

The present study assessed seeking and drinking of a mixed solution (quinine + sucrose) that mimics the taste of ethanol. Prior research has used this solution to study the responsivity to ethanol's sensory properties without the confounding factor of ethanol's pharmacological (e.g., motor-activating or depressing) effects (Bachmanov et al., 2003; López & Molina, 1999), and the influence of the maternal odor in the testing situation. The hypothesis of our study was that stimulation with a pre-exposed, biologically relevant odor (i.e., mother's odor), would enhance seeking (i.e., grasping of the nipple) and drinking of a solution that mimics the taste of alcohol. Four-day-old rats were given access to a nipple providing sucrose+quinine, either with or without the anesthetized mother. A second experiment replicated the procedure but added further controls (i.e., animals stimulated with the odor of another, unrelated mother and animals given only water at test). At the age studied rats discriminate between different tastes, and even more noteworthy, they adjust the intake behavior depending on taste offered (e.g., sweet, bitter) and on the different concentrations of the solutions (Kamenetzky et al., 2015; Miller & Spear, 2008, 2009, 2010). Consistent with this factor, researchers found that 3-hour-old pups regulate intake behavior according to the taste and the nutritional value of food (Nizhnikov, Petrov, Varlinskaya, & Spear, 2002; Petrov, Nizhnikov, Kozlov, Varlinskaya, Kramskaya, & Spear, 2004).

This current investigation provides valuable information on understanding how the olfactory and gustatory systems work in unison during early life and how this interaction can influence alcohol intake.

General methods

Subjects

Eighty-seven 4-day-old Wistar rats were used. The animals, male and female, were derived from 18 dams, mated at the vivarium of Instituto de Investigaciones Médicas Dr. Alfredo Lanari (IDIM-CONICET, Argentina) and given *ad libitum* access to water and lab chow (Cooperación, Buenos Aires, Argentina). The litter representation and number of subjects in each experiment were as follows: Experiment 1 – 24 animals derived from six litters, 12 animals in each group; Experiment 2 – 63 animals, 12 litters. The day of parturition was considered PD 0 and, within each litter, only one male or female was assigned to a given treatment condition (Holson & Pearce, 1992). The vivarium had a 12-h/12-h light/dark cycle, with lights on at 7:00 am, and controlled temperature (22°C) and humidity. Rats used in these experiments were maintained and treated in accordance with the Guide for the Care and Use

of Laboratory Animals by the National Research Council (1996). The experimental protocol (N 010-14) was approved by the institutional animal care committee (CICUAL).

Apparatus

Surrogate nipple The surrogate nipple was cast from rubber latex (AMACO rubber latex, Indianapolis, IN, USA) and molded into a conical form to measure 12 mm long with a rounded tip measuring 1 mm in diameter and the base measuring 2.5 mm in diameter. The base of the surrogate nipple was attached to the end of an angled dental probe to facilitate presentation by the experimenter (Petrov, Varlinskaya, & Smotherman, 1997). Polyethylene tubing (Clay Adams, Sparks, MD, USA) run throughout the length of the nipple. The tubing was attached to a syringe, which was filled with the corresponding solutions. The nipple was in continuous contact with the mouth of the animal, which was gently stimulated on the lips with the tip of the device. The pressing of the nipple by the pup's mouth was associated with a negative pressure that in turn allowed voluntary intake. The pup was clamped in a semi-supine posture into a "vest" fashioned out of ultra-thin, elastic rubber. This light restraint prevented righting attempts but did not otherwise produce discomfort nor hinder the pup's movements.

Solution

The nipple delivered a mixture of quinine and sucrose, which has been shown to emulate the taste of alcohol (Di Lorenzo et al., 1986). Following previous studies (Arias & Chotro, 2005a; Diaz-Cenzano & Chotro, 2010; López & Molina, 1999), this solution was prepared by diluting sucrose 0.1 M + quinine 0.0001 M (Sigma-Aldrich, Buenos Aires, Argentina) with distilled water.

Procedure

Experiment 1: Testing responsiveness to a surrogate nipple providing a solution that emulates the taste of alcohol (i.e., sucrose and quinine) in the presence of the mother's odor

We explored the effects of the mother's odor on attachment to an artificial nipple delivering a solution that mimics the taste of alcohol. Two groups were stimulated for 6 min with the artificial nipple providing this sweet and bitter solution in the presence (Odor Group) or absence (No odor Group) of the dam. The test involved delivery of the quinine-sucrose solution via the artificial nipple in the presence (Odor Group, the anesthetized dam was about 2 cm away from the nose of the pup) or absence (No-odor Group) of the mother's odor.

Experiment 2: Responsiveness toward a surrogate nipple providing sucrose-quinine or water in the presence of the own mother's or another mother's odor

In Experiment 1 the experimental, but not the control, pups were exposed to the odor provided by an anesthetized mother. There was no physical contact between the pups and the dam, yet the pups were exposed to the social stimulus and to the heat provided by the dam. It was not clear, then, if the odor was the only factor inducing differential responsiveness to the nipple. Experiment 2 controlled these confounding factors by assessing responsiveness to the nipple in the presence of the anesthetized mother or in the presence of another, unrelated, anesthetized dam. Moreover, to assess the specificity of the promoting effect of the dam on nipple attachment, a sub-group of pups was offered water, instead of the sucrose-quinine mixture, through the nipple. A 2 (female present during the test: own mother or another mother) \times 2 (solution given via the nipple) factorial design was employed in Experiment 2. Each of the four groups had 15–16 animals. The dams (related and unrelated) were at the same postpartum day.

In both Experiments, the test was performed between 9 a.m. and noon. At DP 4, the dam was anesthetized with a mix of ketamine (40 mg/kg) and xylazine (5 mg/kg). The pups were then placed into a heating chamber (kept at 35 °C; Simen, Buenos Aires, Argentina) and, 15 min later, gently stimulated in the urogenital region with cotton to induce urination and defecation. Each animal was weighed, equipped with the vest, and attached to a tempered mirror. The experimenter stimulated the perioral area of the pup with the tip of the surrogate nipple. The oral grasp response, which allowed suckling and hence access to the solution, involved an active movement of the pup's head toward the surrogate nipple, which resulted in the tip of the nipple entering the oral cavity and the mouth closing around it. From this response the following measures were obtained: latency to grasp, total time spent on the nipple (sum of the duration of all grasps), frequency of grasps (attachments initiated), and mean duration of an individual grasp response (total time of grasps/number of grasps). The consumption of the solution was measured via the percentage of bodyweight gain: [(post-testing weight – pre-testing weight)/pre-testing weight * 100].

All experiments were videotaped and subsequently analyzed by two observers (observer's reliability > 85%) who were blind to the experimental conditions.

Data analysis

In Experiment 1 each variable was analyzed using a t-test for independent samples. The grouping factor was the odor condition during the test (mother's odor or no-odor exposure). Between-group analyses of variance (ANOVAs) were employed in Experiment 2. Odor condition (own mother's odor or other mother's odor) and Solution (sucrose-quinine or water) were the independent factors. Significant interactions were further

analyzed by Tukey's HSD *post hoc* comparisons, and planned comparisons were used when justified by *a priori* hypotheses. Data were collapsed across sex since, across variables, this factor exerted no significant main effect nor interacted with the remaining variables. The alpha level was set at ≤ 0.05 .

Results

Experiment 1

Figure 1 shows latency to grasp the nipple, number of grasps, total time of grasps, mean of grasp duration, and percentage of bodyweight gain during the test. It seems that the presence of the mother significantly facilitated approach and contact with the nipple. The statistical analysis supported these observations. Subjects evaluated in the presence of the mother showed, when compared to animals in the no-odor group, significantly greater total time attached to the nipple, $t_{22} = 4.81$, $p < .00008$, number of

grasps, $t_{22} = 4.14$, $p < .0004$, mean duration of grasps, $t_{22} = 3.02$, $p < .01$, and a significantly lower latency to grasp the nipple, $t_{22} = -5.71$, $p < .00004$. Percentage of bodyweight gained was greater in the odor versus the no-odor group, but this difference did not reach statistical significance ($p > .05$).

Experiment 2

Figure 2 illustrates the behaviors measured in Experiment 2. The ANOVA for percentage of bodyweight gain revealed a significant interaction between odor condition and solution, $F_{1, 59} = 7.60$, $p < .01$. The *post hoc* tests revealed significantly greater intake of sucrose-quinine than water in those pups stimulated with the odor of the mother. On the other hand, the *post hoc* tests indicated that pups stimulated with the odor of an unrelated dam consumed as much sucrose-quinine as water. Also of importance, intake of sucrose-quinine was significantly greater in the presence of the related dam than in the presence of the non-related dam.

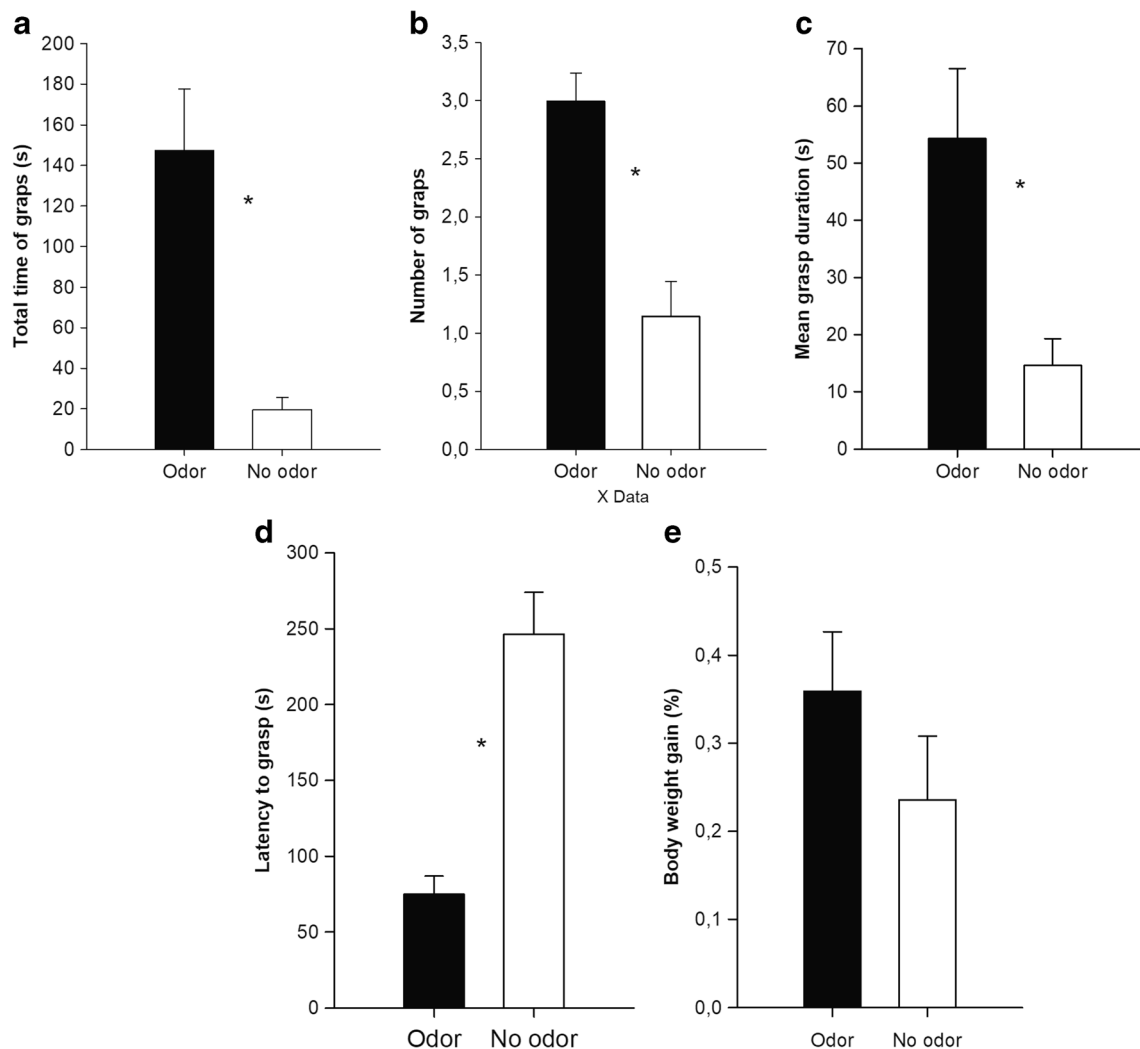


Fig. 1 Mean (\pm SE) of (a) total time grasp, (b) mean grasp duration, (c) number of grasps, (d) latency to grasp, and (e) percentage of body weight gained, during the 6-min presentation of the artificial nipple containing quinine and sucrose solution. *Indicates p values $< .05$

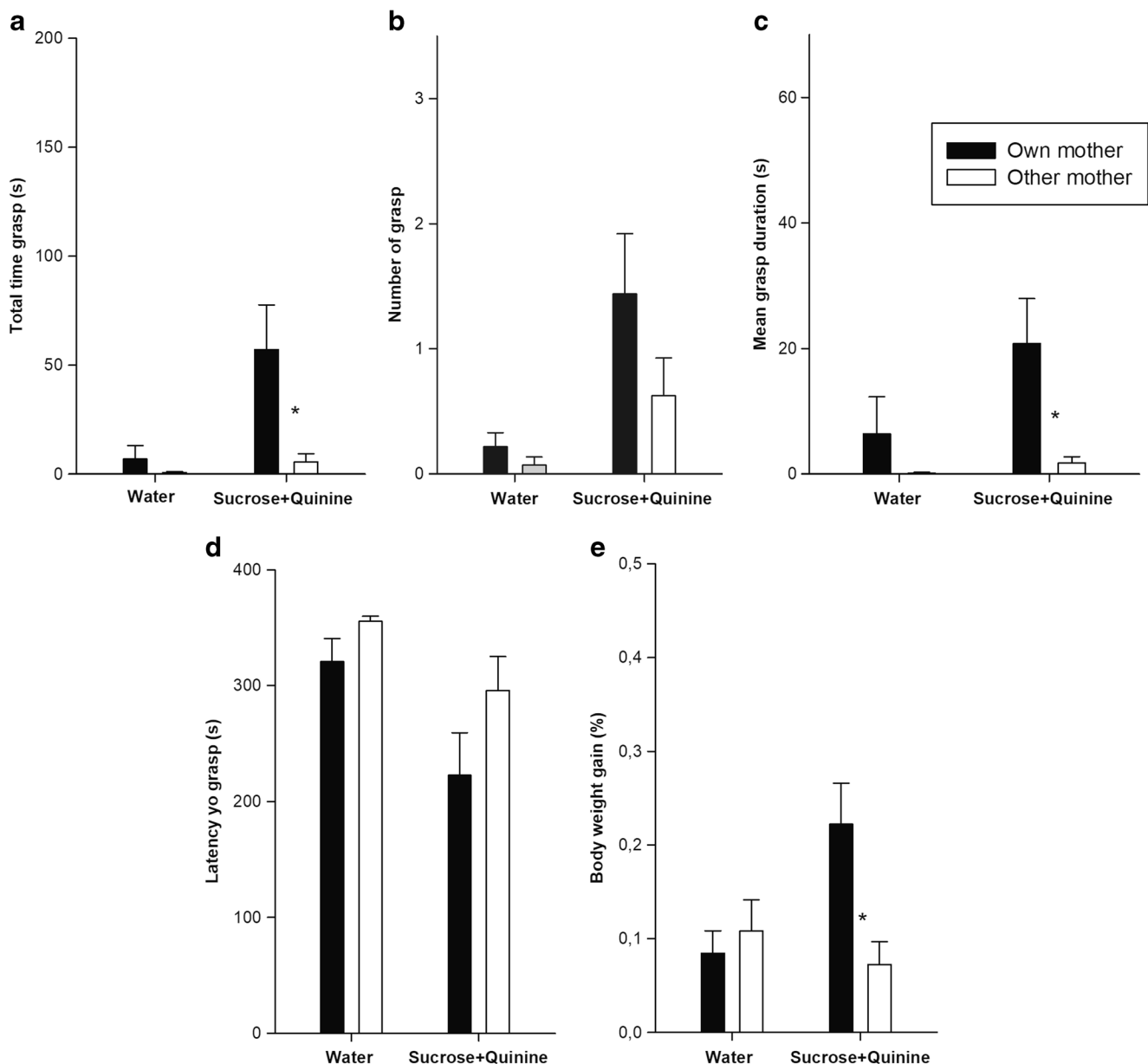


Fig. 2 Mean (\pm SE) of (a) total time grasp, (b) mean grasp duration, (c) number of grasps, (d) latency to grasp, and (e) percentage of body weight gained, during the 6-min presentation of the artificial nipple containing

water (left bars) or quinine and sucrose solution (right bars). *Indicates p values $< .05$

The ANOVAs for total time spent grasping the nipple and mean grasp duration indicated a lack of significant main effects or significant interactions. Figure 2 suggests, however, an exacerbated response in the group given sucrose-quinine compared with the other groups. Guided by these impressions, and by our *a priori* hypotheses, we conducted planned comparisons and observed significantly greater time spent on the nipple ($F_{1, 31}=4.06$, $p < .05$) and mean grasp duration ($F_{1, 31}=4.14$, $p < .05$) in the group that received the sucrose+quinine solution in the presence of their own mother than in the group assessed in the presence of another mother. Number of grasps and latency to grasp were not affected by the factors under analysis ($p > .05$).

Discussion

Studies have shown that early on neutral odors (e.g., cineole) elicited alcohol intake in rat pups following pairings with ethanol (Abate, Spear, & Molina, 2001; March, Abate, & Molina, 2009). The most important new information gained from the present study is that 4-day-old rats tested in the presence of the mother (and hence exposed to maternal odor cues previously experienced *in utero*) exhibited enhanced seeking and intake of a solution that mimics the chemosensory, but not the post-absorptive, properties of ethanol. This suggests that, during the neonatal period, the mere presence of familiar odors may facilitate

acceptance of flavors with aversive components (i.e., bitter taste), and therefore may act as a permissive factor for ethanol seeking and intake.

In Experiment 1, the experimental group had access to a heat source and social contact via the anesthetized dam. Experiment 2 included control animals stimulated with the odor provided by an anesthetized, yet unrelated, dam, and thus dispelled the alternative explanations for these issues. The animals assessed in the presence of their mother exhibited a greater percentage of bodyweight gain and performed significantly more responses toward the artificial nipple than those assessed in the presence of an unrelated dam. This difference was not observed when the artificial nipple dispensed water, suggesting that the promoting effect of pre-exposed odors upon fluid seeking and intake is expressed only when the solutions have an aversive component. These results replicate studies in newborn rats (Kamenetzky et al., 2015) that reported greater intake and grasp responses to an artificial nipple (scented with a pre-exposed lemon odor) that dispensed a moderate concentration of quinine, but not to a nipple providing sucrose. The present study generalizes this phenomenon to a biologically relevant odor (i.e., mother's odor), and to a solution that emulates the taste of a drug of abuse (ethanol) that can be readily transferred to breast milk after maternal intoxication.

The taste of milk can be altered by the diet ingested by the mother. It has yet to be assessed how the tastes experimented with in the maternal milk could interact with previously learned odors that are present in the suckling context. Studies with human babies, however, showed that when mothers consume a capsule of garlic, babies display greater response towards the breast (Mennella & Beauchamp, 1991b; Mennella & Beauchamp, 1993b). In addition, babies who were exposed to milk containing alcohol consumed more of the breast milk compared to babies exposed to uncontaminated milk (Mennella, 1999; Mennella & Beauchamp, 1991a). In light of these results, it is interesting to hypothesize that odors present in the context of breastfeeding could modulate responses to the maternal breast when the following two conditions are met: (1) a familiar odor is present and (2) a substance with a bitter taste is offered.

Several pre-clinical (Fabio et al., 2013; Molina, Spear, Spear, Mennella, & Lewis, 2007) and epidemiological (Dawson et al., 2008; Jenkins et al., 2011; Windle & Windle, 2012) studies indicate that early exposure to ethanol increases subsequent acceptance of this drug. These studies have analyzed several factors that can modulate the effect of early-onset ethanol use upon subsequent ethanol abuse and dependence (e.g., dose of first ethanol exposure). Yet, little attention has been devoted to date to the interaction of the taste of the drug with other, familiar or non-familiar, odors in combination with ethanol access. The results of the present study show that a biologically relevant pre-exposed odor, the scent of the own mother, enhanced the acceptance of the sucrose-quinine mixture. The sweet component of ethanol has been traditionally thought to induce or

facilitate alcohol consumption, yet the data from this research and those obtained by Kamenetzky et al. (2015) suggest that the bitter component could also play an important role, particularly early in life in the context of breastfeeding. This is a preliminary hypothesis that requires more evidence to be confirmed.

It has been shown that experimental contamination of amniotic fluid with alcohol increases later, postnatal, consumption and palatability of that substance (Arias & Chotro, 2005a, 2005b). It can be proposed that, in those experiments, the animals went through the two stages of our protocol. In phase 1, the animals were naturally pre-exposed to the mother's odor during the last stage of gestation. In phase 2, in turn, the animals were exposed to ethanol through amniotic fluid that also provided exposure to the mother's odor. When tested postnatally, these pups exhibit, akin to those in the present report, greater acceptance of alcohol or alcohol-related cues. A large body of evidence shows that both human (Mennella, Jagnow, & Beauchamp, 2001) and rat (Abate, Pueta, Spear, & Molina, 2007; Chotro & Arias, 2006) fetuses are capable of perceiving odors present in the amniotic fluid during the last stage of gestation. The present results suggest that the intake of amniotic fluid contaminated with alcohol is enhanced in these subjects, due to the interaction of the bitter taste and maternal odor.

In summary, our results indicated that the presence of maternal odor significantly enhanced attachment to, and intake from, an artificial nipple dispensing a solution that emulated the taste of alcohol. It is noteworthy that the sucrose-quinine mix employed was novel, which indicates that these results cannot be the consequence of previously learned associations involving such taste.

This study contributes to the little explored area of the interaction between olfaction and taste during early ontogeny. The results are consistent with previous work from our laboratory in which 3- or 12-day-old rats exhibited an increase in the consumption of a bitter solution when tested in the presence of their own mother, but not when tested in the presence of another, unrelated, dam (Ifrañ, Suárez, Pautassi, & Kamenetzky, 2018). It seems that these early experiences are key for the development of eating habits or the consumption of psychoactive substances. The animal model outlined in the present study should be useful for assessing strategies aimed at solving problems related to the early rejection or acceptance of unpalatable substances, including those subjected to abuse.

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