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Alcohol odor elicits appetitive facial expressions in human neonates prenatally exposed to the drug

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HIGHLIGHTS

- Newborns, prenatally exposed to alcohol, recognize the drug's odor.
- Alcohol odor recognition is evidenced through appetitive facial expressions.
- Maternal levels of alcohol consumption predict the hedonic response to alcohol odor.

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ABSTRACT

Specific memories arise during prenatal life as a function of fetal processing of chemosensory stimuli present in the amniotic fluid. Preclinical studies indicate that fetal exposure to alcohol modifies subsequent neonatal and infantile responsiveness towards the sensory attributes of the drug. It has been previously demonstrated that 1–2 day-old human neonates recognize ethanol odor as a function of moderate maternal alcohol consumption during gestation. In the present study 7–14 day-old newborns were assessed in terms of behavioral responsiveness to alcohol's chemosensory attributes or to a novel odor (lemon). These newborns were representative of mothers that exhibited infrequent or frequent alcohol drinking patterns during pregnancy. Different clinical assessments indicated that all newborns did not suffer congenital or genetic diseases and that they were completely healthy when behaviorally evaluated. Testing was defined by brief presentations of ethanol or lemon odorants. Two sequences of olfactory stimulation were employed. One sequence included five initial trials defined by ethanol odor stimulation followed by one trial with lemon and five additional trials with the scent of the drug (EtOH–Lem–EtOH). The alternative sequence (Lem–EtOH–Lem) was primarily defined by lemon olfactory exposure. The dependent variables under analysis were duration and frequency of overall body movements and of facial expressions categorized as aversive or appetitive. The main results of this study were as follows: a) at the end of the testing procedure and independent of the sequence of olfactory stimulation, babies born to frequent drinkers exhibited signs of distress as operationalized through higher durations of aversive facial expressions, b) despite this effect, babies born to frequent drinkers relative to newborns delivered by infrequent drinkers exhibited significantly higher frequencies of appetitive facial responses when primarily stimulated with ethanol odor (EtOH–Lem–EtOH sequence) and c) when merging both samples of babies, a positive and significant correlation was found between overall maternal absolute alcohol consumption per month and frequency of appetitive facial expressions elicited by alcohol odor. In conjunction with previous preclinical research, the present results indicate that human prenatal exposure to the drug that yields no evident teratological effects is sufficient to modify the hedonic value of alcohol's chemosensory attributes.

1. Introduction

From a neuroethological perspective there is consistent evidence that supports the hypothesis of prenatal programming of postnatal specific appetites [1–3]. Depending on the nature of the appetite under consideration, different mechanisms seem to program the developing brain in terms of acceptance or rejection of a given chemosensory stimulus

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that will later define feeding or searching patterns of a palatable substance. For example, both in rats and humans, extracellular dehydration during pregnancy is sufficient to induce a remarkable increase in the offspring's salt appetite that can persist until adulthood [2]. Fetal chemosensory processing of biological and non-biological cues present in the prenatal milieu also exerts profound postnatal changes in terms of how the neonate reacts to these specific stimuli. Human newborns (2–4 days old) evaluated through olfactory orientation tests detect the smell of the amniotic fluid and of a milk formula with which they were fed. Yet, when both odorants are presented in a two-way preference test, the prenatal substrate elicits more behavioral orienting responses than the postnatal olfactory-related feeding substrate [4]. In terms of non-biological chemosensory cues, it has been reported that maternal consumption of anise flavor during pregnancy results in a significant neonatal preference for this odor [5].

Due to the teratogenic properties of ethanol, the link existing between this drug and early development has been primarily analyzed from the perspective of its deleterious morphological and neurobehavioral consequences [6, 7]. Animal research has also emphasized that prenatal exposure to the drug represents a critical factor when considering subsequent ethanol affinity as operationalized through exacerbated drinking, active behavior in search of the drug coupled with heightened sensitivity to its reinforcing effects as well as those centrally exerted by its main metabolite (acetaldehyde) [8–11]. These phenomena have also been reported in human epidemiological studies even when controlling for other variables known to affect ethanol use and abuse (e.g., genetic predisposition as assessed through family history of alcoholism, gender, co-use of other drugs during pregnancy and different environmental factors) [12–16].

A significant fraction of the studies concerning mechanisms through which early alcohol experience drives later ethanol affinity has been conducted through the use of altricial subprimates such as the rat. In this species, acute alcohol contamination of the amniotic fluid during late gestation is sufficient to recruit fetal processing of the drug's olfactory and gustatory cues. This experience, implying a technical approach that avoids fetal alcohol intoxication, is sufficient to promote neonatal and infantile recognition and acceptance of the odor and taste of the drug [17–19]. Furthermore, during developmental stages analogous to the second and third gestational trimester in humans, rats acquire appetitive associative memories comprising salient olfactory stimuli and ethanol's or acetaldehyde's reinforcing effects [11, 20, 21]. Hence, early familiarity with ethanol's sensory cues or the association of these stimuli with the drug's reinforcing effects has been proposed as two congenital mechanisms that determine or modulate subsequent ethanol preference or drinking patterns [8–11].

Relative to possible ethanol-related learning during human fetal development, the literature is scarce; particularly when considering the hedonic component of acquired memories. The prolific work of Mennella and Beauchamp has shown that during lactation babies are capable of processing small concentrations of ethanol in maternal milk and that this experience enhances alcohol odor preferences (e.g.: [22–25]). As stated, when non-toxic substances (e.g. anise) are incorporated in the maternal diet during pregnancy, the hedonic polarity (appetitive versus aversive responding) changes when the neonate is re-exposed to this odorant [5]. To our knowledge, in terms of maternal alcohol ingestion during pregnancy and its impact upon neonatal responding to ethanol odor, only one study has been conducted [26]. Healthy neonates (24–48 h. old) born to moderate or social drinkers were exposed to the scent of the drug or a novel artificial odorant (lemon). When initially exposed to alcohol odor, these babies exhibited significantly higher levels of motor activity relative to age counterparts delivered by mothers who infrequently drank ethanol during gestation. The overall results of this study suggested that intrauterine ethanol experiences promoted behavioral recognition of the scent of the drug without affecting patterns of responsiveness to a novel olfactory cue. These results are analogous to those reported in subprimates prenatally exposed to subthreshold ethanol doses relative to its teratogenic effects [17–19, 27]. Yet, the dependent variables utilized in the human study did not allow examining possible hedonic responsiveness elicited by ethanol's sensory attributes.

Neonatal facial responsiveness to taste and smell seems to function as social cues to communicate emotions [28]. Newborns show expressions of pleasure or grimacing in response to sweet and bitter tastes, respectively [29–33]. In an early study performed by Rosenstein & Oster [34], neonatal facial expressions in response to basic tastes (sour, salty, sweet and bitter) were analyzed using the Baby Facial Action Coding System (BFACS), an adaptation of the FACS technique elaborated by Ekman and Friesen [35]. The authors reported that 2 hour old babies differentiated sour and bitter as well as sweet from non-sweet solutions. It has also been observed that 3-day-old humans mainly exhibit disgust facial reactions when confronted with an odorant judged as aversive by adult raters [36].

The present study was conducted with mothers and babies representative of the same population where we previously observed differential responsiveness to ethanol odor as a function of prenatal drinking patterns [26]. In this opportunity, babies were tested when the mother brought them to the hospital for their first pediatric examination. Hence, one of the questions under analysis was whether older newborns (7–14 days old) relative to the ones originally tested (1-2 days old) [26] still exhibited differential behavioral responding (overall motor activity and facial expressions) to ethanol odor as a function of frequent or infrequent drinking during gestation. Considering that neonates, innately or through prior learned experiences, exhibit specific facial reactions when confronted with certain chemosensory or nociceptive stimuli, we also assessed expressions qualified as appetitive or aversive [26, 34, 35, 37, 38]. Hence, a major goal in the present study was to analyze whether human alcohol experience in utero shapes early alcohol memories characterized by a particular emotional content. Obviously this goal is not independent from the one regarding temporal persistence of differential responding to the smell of the drug as a function of maternal drinking history. It adds alternative modes of expression of possible memories generated in utero through the analysis of specific gestures characterized by either appetitive or aversive emotional contents. It is important to emphasize that in our original study [26] only gross behavioral reactivity was employed as a dependent measure while there was an absence of a more thorough ethological analysis of particular facial expressions that can reveal emotional-related contents of the memories generated during pregnancy. The results will be presented following an analytical sequence that first scrutinizes the gross overall behavioral reactivity to ethanol odor or a novel olfactory cue (lemon). As will be observed and later discussed in detail, the pattern of gross behavioral responsiveness to the smell of the stimuli here employed does not reveal in 7–14 day-old-babies differential action patterns indicative of specific memories linked with maternal drinking habits. The second major block of results is centered in the analyses of facial expressions, either appetitive or aversive, elicited by the odorants under consideration; an experimental approach which was not utilized in younger babies [26]. A first step in this approach implies an inferential analysis of all the behaviors categorized as either appetitive or aversive as a function of maternal drinking patterns and olfactory cues presented to the babies. Subsequently, each particular gesture, being appetitive or aversive, will be analyzed in detail. Finally, correlational analyses will be utilized to examine the strength of the association existing between monthly consumption of ethanol in each particular mother and the magnitude of emotional responsiveness in their corresponding babies.

2. Material and methods

2.1. Assessment of maternal alcohol consumption

Alcohol consumption patterns during pregnancy were assessed through the use of a brief questionnaire that evaluates frequency,