Prenatal and Early Determinants of Ingestive Behaviors

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Abstract

A hostile prenatal environment and exposure to various stimuli in utero can significantly impact development. This occurs specifically in the case of development of the taste system, where the smell and taste of foods can be transported to the intrauterine environment specifically through the amniotic fluid. This exposure can then modulate preferences and aversions, long-term, in both human and non-human animals. The purpose of this review is to provide an overview of the current understanding of how prenatal exposure to different environments can lead to long-term changes in the taste system, as well as to understand the impacts of such changes. The present review offers an overview of the current research involving impacts of prenatal exposure on aversion and preference development in rats, as well as human models.
Prenatal and Early Determinants of Ingestive Behaviors  

The prenatal period is an extremely sensitive period where environmental stimuli can alter the course of the offspring’s life by influencing modulations in terms of behavior, neurochemistry, and cognition, among other effects. These impacts on the intrauterine environment can have effects that last much longer than the incubated gestational period. Research has shown impacts of countless environmental toxins and exposures on postnatal life, in both rats and humans. In rats, the gestational period lasts approximately 22 days, with development from blastula to gastrula occurring within days five to eight and embryo to fetus occurring from approximately days 12 to 18 (Witschi, 1956). In humans, the gestational period is significantly longer, lasting approximately 38 to 40 weeks and being characterized by more pronounced stages of specific development. The shortened period in rats allows for unique studies that can discern the effects of exposure to specific environmental stimuli in hopes of applying similar concepts to human models.

The ability to perceive flavors and subsequently learn preferences and aversions to these flavors begins in utero with the development of the gustatory and olfactory systems. These systems work hand in hand, and are unique in that they are two of the senses that can be modulated and changed in utero from conception. Both these sensory systems are developed and have achieved adult-like function by the end of gestation, in both rats and humans (Ventura & Worobey, 2013). Flavor perception occurs due to the integration of our sense of smell and sense of taste, which allows activations to occur within the gustatory system that allow for a sense of salt, sweet, bitter, umami, or sour. Additional evidence has also suggested the presence of a possibility for taste cells specific to fat and calcium tastes as well. Development of these individually unique taste cells begins during the first trimester, where the fungiform, foliate, and
circumvallate papillae appear by the 10th week of gestation, and by the beginning of the second trimester, these taste papillae are functionally mature, similar to adulthood. Similarly, the olfactory system begins developing during the first trimester, where by the eighth week the olfactory bulb has differentiated from the forebrain, and by the 28th week, olfactory marker proteins occur as a sign of olfactory receptor maturity (Ventura & Worobey, 2013). These developments come together to allow for the perception and learning of stimuli that are exposed to the fetus through the uterine environment. When a gestating mother consumes a specific food, the smell and taste of this food can be transmitted to the uterine environment, specifically through the amniotic fluid. This has been shown in studies showing that odor of amniotic fluid was altered by consumption of various foods and tastes (Mennella, Johnson, & Beauchamp, 1995). This exposure allows for the prenatal shaping of preferences and aversions in terms of olfactory and taste stimuli, which begin occurring even before the postnatal period.

Prenatal exposure to stimuli in the intrauterine environment allows for learning to occur by the fetus. This learning can lead to taste aversions, which may ultimately present themselves in the case of conditioned taste aversions, food neophobia, or food pickiness. Conditioned taste aversions act as a much more implicit form of aversion learning, where exposure to a taste stimulus, when paired with an emetic stimulus, can lead to the learning of an aversion to the original taste. The origins of food neophobia and food pickiness are more complex, usually involving exposure to various food groups, as well as other environmental variables. Food neophobia can be defined as an avoidance or anxiety towards new foods, which opposes food neophilia, or the tendency to acquire preference towards new foods. Food pickiness, however, is defined as consuming an inadequate variety of foods and rejecting both specific familiar and unfamiliar food types. This is similar in definition and is often used interchangeably with food
fussiness, which also describes an unwillingness to eat a wide variety of foods (Dovey, Staples, Gibson, & Halford, 2008).

In the same way, exposure to taste stimuli in utero can lead to the development of preferences, simply due to exposure. The mere-exposure effect occurs where increased exposure to a stimulus often results in increased familiarity and therefore increased preference for that stimulus. Through exposure in the intrauterine environment, preferences for certain taste stimuli over others can start to develop in utero, which impacts postnatal eating behaviors in both rats and humans.

Whether through the development of preferences or aversions, the prenatal environment offers a significant impact on postnatal acceptability of taste stimuli. Aversions, therefore, may consequently lead to a lack of a varied diet, particularly in children who often refuse to eat vegetables and fruit, which ultimately leads to a diet that lacks the appropriate amounts of these food groups. Preferences, on the other hand, may lead to the development of increased ingestion of particular food groups, which can ultimately progress to disease later in life. Therefore, the presence of a hostile uterine environment, or uterine environment characterized by increased exposure to certain stimuli, may ultimately shape preferences and aversions in such a way that may lead to the development of metabolic disorders and ultimately lead to the development of disease. Considering this, the presence of a hostile intrauterine environment may play a significant role in the growing trend of obesity around the globe. For this reason, an examination of the potential prenatal effects behind the development of preferences and aversions is necessary in order to increase an understanding of how the prenatal environment may shape postnatal food related behaviors depending on hostility, exposure, or associations.

Rats
Taste Aversions

Acquisition of a conditioned taste aversion (CTA) in rats has been well documented as early as one day old. However, the timeline of successful acquisition of a prenatal CTA in rats remains a current topic of investigation. An understanding of the nature by which these aversions occur and what factors influence them is currently developing. This section will examine the effect of alcohol, anesthetics such as ketamine, or other drugs such as methamphetamines in the intrauterine environment and their subsequent effect on modulating taste aversions. Additionally, other stimuli that may already be present in the intrauterine environment, such as testosterone, or stimuli that may occur outside of the uterus and act to modulate taste aversions, will be discussed. Finally, the section will conclude with a brief discussion of the types of aversions that might be acquired, specifically examining their adaptive nature, as well as a discussion of the timeline of acquisition of learning that may occur within the uterine environment.

One of the first investigations of how taste aversions in rats may be modulated by prenatal environment involved the presence of alcohol in the uterine environment. In line with this, Riley, Barron, Driscoll, and Chen (1984) showed that rats exposed to ethanol during the prenatal period showed significant impairment in forming a conditioned taste aversion. Pregnant dams were separated into three groups: liquid diet 35% ethanol, liquid diet 0% ethanol, and control lab chow. Pups either five days old or 15 days old were given either saccharine and NaCl (control) or saccharine and LiCl. Animals were infused with saccharine solution 12 hours later to assess changes in intake. At five days of age, there was no difference in consumption of saccharine in rats exposed to a conditioned taste aversion paradigm compared to controls, suggesting no acquisition of a CTA. At 15 days of age, pups exposed to ethanol during the prenatal period showed significantly more consumption of saccharine compared to controls,
suggesting less of a CTA developed. The hippocampus in the rat develops to a large extent during the postnatal period and in particular, there is a rapid period of development in the dentate gyrus at about two weeks of age. Because of this, it is possible that rat fetuses exposed to ethanol in the prenatal period have stunted development in terms of hippocampal neurons. This may lead to the prevention of learning, particularly in the case of learned aversions. Additionally, prenatal exposure to ethanol has been shown to lead to more extensive alterations in feeding behaviors. Gabriel and Weinberg (2001) showed this, revealing that prenatal exposure to ethanol leads to altered feeding behaviors and weight deficiencies, including failure to successfully attach to nipple and altered suckling behaviors, as well as lower birth weight and difficulty maintaining or gaining weight over infancy period. Exposure to ethanol leads to decrease in overall food neophobia, with significant increased preference towards ethanol and sucrose. Dams exposed to ethanol show significantly longer pregnancies but produce significantly smaller litters, both in terms of number and weight. Rats exposed to ethanol showed longer latencies to attach to nipple and failure to nipple shift. These disturbances in eating behaviors ultimately lead to significant difficulties and consequences during the postnatal developmental period that can extend beyond adolescence and adulthood.

Research has also revealed contradicting evidence on whether doses of ethanol, when given to rats, induce appetitive or aversive motivational effects. This paradox has shown to be influenced by a variety of variables. Arias, Pautassi, Molina, and Spear (2010) investigated this, analyzing disgust reactions elicited by a high ethanol dose in preweanling rats to determine whether ethanol can be used as a CTA agent in a similar manner to LiCl. Results suggested that pups given paired presentations of saccharin and the aversive agents (ethanol or LiCl) consumed less saccharin during the first testing day than controls. These pups also showed more aversive
behavioral reactions to the gustatory conditioned stimulus than controls. Specifically, increased amounts of grooming, general activity, head shaking, and wall climbing as well as reduced mouthing were observed in response to the conditioned stimulus. Overall, these results suggest that a taste conditioned stimulus paired with postabsorptive effects of ethanol and LiCl elicited a similar pattern of conditioned rejection reactions in preweanling rats. These results suggest that similar mechanisms may be underlying CTAs induced by LiCl and a relatively high ethanol dose. Additionally, these results suggest that whether ethanol induces an aversive or appetitive influence is dependent upon the dosage. This has important implications for the exposure to ethanol in utero, where differing concentrations may lead to differing effects and symptoms, which may ultimately be determinants of specific behaviors throughout life.

Similarly to ethanol exposure, taste aversions in rats have been modulated by exposure to other drugs or toxins. One such drug includes ketamine, which has been thoroughly investigated as a possible anesthetic that may impact taste development in rats. Mickley, Lovelace, Farrell, and Chang (1995) exposed pregnant rats to different types of anesthesia and a conditioned taste aversion paradigm. Saccharine avoidance was most prominent in rats that learned the CTA following injection of ketamine. This data suggests that ketamine can act to modulate learning and taste aversions and that they are not uniform in their ability to influence the outcome of conditioning. A partial explanation for these results may be the fact that NMDA receptor activation plays an important role in early neuronal development. Supporting this in a follow-up study, Mickley and colleagues (1998) showed that when rat pups underwent a taste aversion conditioning procedure using ketamine, an NMDA receptor antagonist, results showed that ketamine could block the formation of a CTA in neonatal rats. Rats given neonatal ketamine licked more towards saccharine even after pairing with LiCl. Ketamine may reduce the ability of
the neonate to sense the sweetness of the saccharine or to experience the malaise produced by the LiCl. Most likely, ketamine blocks learning by blocking NMDA receptors and prevents the acquisition of a CTA. Mickley and colleagues (2014) showed this, revealing that rats exposed to allicin (garlic) in utero developed a CTA when paired with LiCl. When exposed to ketamine, aversion effect was eliminated. Ketamine acts as an NMDA blocker, which ultimately may act to block learning and specifically conditioned taste aversion learning to affect latent inhibition. Overall, this suggests that rats are able to form an aversion in utero if exposed to the right conditions.

While ethanol and ketamine show significant effects in the development of taste aversions, research has implicated other drugs in aiding in attenuating aversions. Such research has implicated methamphetamines as having a significant effect on aversions, acting similarly to ethanol. Rorabaugh, Seeley, Evans, Marengo, and D’Souza (2017) exposed pregnant rats to methamphetamines or saline as a control. Following birth, pups were exposed to a nicotine CTA paradigm. In this paradigm, nicotine is paired with a pleasant stimulus as an aversive stimulus, in order to examine sensitivity to the aversive effects of nicotine. Male rats exposed during the prenatal period to methamphetamines showed decreased aversion to nicotine, whereas no difference was shown in aversion in females. Adult male rats exposed to methamphetamine in the prenatal period may be more vulnerable to nicotine addiction due to decreased sensitivity to the aversive effects of nicotine. Prenatal methamphetamine exposure leads to decreased levels of dopamine markers in striatum of males. Dopamine neurotransmission mediates the aversive effects of nicotine in the nucleus accumbens, which modulates the pleasurable response. This may suggest that methamphetamine exposure leads to a dysregulated reward pathway in males specifically, changing the neurochemistry of how these drugs are processed in the brain. The
mechanism behind why this uniquely affects males is up to investigation, however, many studies have implicated the role of the estrous cycle in possibly leading to some of these unique differences.

Research has suggested other environmental factors that may influence prenatal learning of a taste aversion. For instance, Babine and Smotherman (1984) suggested that intrauterine exposure to testosterone might lead to modulated taste behavior, specifically in terms of aversions. In this study, rat pups were exposed to testosterone in utero. Males took significantly longer to extinguish a learned taste response when compared to females. Testosterone injection significantly delayed extinction rate of females that had caudal males in their litter, suggesting that this group is more susceptible to testosterone manipulation. Therefore, testosterone has shown to speed up acquisition and slow down extinction rate of a CTA, when present at the time of conditioning. This reveals the role of gonadal hormones in learning and specifically, taste aversion learning. Although the mechanism is largely unknown, results have shown that hormones of the pituitary-adrenal system play a large role in the acquisition of conditioned taste aversions, specifically blockage of these hormones can lead to interference in acquisition and adrenocorticotropic hormone injections, ultimately leading to high levels of testosterone, can lead to prolonged extinction.

The development of these taste aversions in rats is also dependent on the food stimulus utilized in the pairing. Normally, rat pups do not form successful taste aversions to milk-borne stimuli, particularly if the presentation of the conditioned stimulus occurs during a nursing episode. This phenomenon may suggest that aversions are influenced by adaptive behaviors, in that the adaptivity of preference for milk may offer a certain amount of protection from acquiring or expressing an aversion to maternal food cues. Pernick and Alberts (1984) investigated this
idea, showing that when weaning was delayed, pups did not demonstrate an aversion to milk compared to pups that were weaned normally. These results may occur due to the fact that prior to weaning, rat pups have no nutritional alternatives. Because of this, it would be disadvantageous for the pup to learn an aversion to a milk-related maternal food cue. Therefore, pups nursed on a delayed weaning schedule are less likely to acquire an aversion to a milk-related stimulus.

However, the acquisition of aversions to usually preferential stimuli has also been shown when paired with LiCl, further indicating rat pups ability to not only sense stimuli presented to the intrauterine environment, but also learn and react to these stimuli in alternative ways. For instance, conditioned inhibition occurs when a conditioned stimulus becomes a signal for the absence of the unconditioned stimulus. For example, in the classic Pavlovian paradigm where a bell indicates the presence of food, a bell followed by a whistle would indicate the absence of food. This learning paradigm has been studied extensively in studies pairing inhibition and conditioned taste aversion. Aranda-Fernandez, Gaztañaga, Arias, and Chotro (2016) investigated this in rats, examining whether conditioned inhibition could be established in infant rats. Rats were given saccharine paired with LiCl, and once the CTA was successfully established, rat pups were given saccharine paired with saline or lemon flavor. Results revealed significant acquisition of a conditioned inhibition to the lemon flavor in males only. Conditioned inhibition can be successfully shown in preweanling rats when using a conditioned taste aversion paradigm. Sex may play a role in the development of this learning process. Female rats at this age failed to acquire conditioned inhibition, or at least failed to express this type of learning under the present experimental conditions. This may be due to the fact that learning of aversions has shown to be different based on sex, specifically in the presence of methamphetamines and testosterone.
Overall, female rats showed a longer latency to acquire aversions overall, which may suggest that the female development predicts more difficulty to acquire aversions. These sex-differences may disappear following development, where adult female and male rats show similar patterns of aversion acquisition.

The specific timeline of rat pups ability to acquire aversions and react to stimuli in utero is also a current topic developing in understanding. Smotherman and Robinson (1985) investigated this specifically, exposing rat fetuses to a mint taste or saline by injection into the amniotic fluid, followed by mint flavor and LiCl in order to determine whether fetuses would respond to a taste or odor cue as a function of its familiarity. Results revealed that rats can acquire a conditioned aversion to mint on Day 17 of gestation and this conditioned aversion can be expressed in utero through its effects on spontaneous fetal behavior. This reveals that chemical modifications of the fetal environment can affect behavior, such that rats are able to produce aversions in utero based on environmental conditions that may affect adult eating behaviors and patterns of behavior in utero and beyond. Natural associations formed in utero may influence postnatal maternal-offspring behavior. Specifically through this, research has shown that the earliest acquisition of a conditioned aversion in rats is day 17 of gestation, however this limit has been determined through very few experiments. In order to gain further insight into the limits of prenatal memory and learning, Gruest, Richer, and Hars (2004) investigated the capacity of the rat fetus to acquire memory in a CTA paradigm on gestational day 15 to 16 or 18 to 19 and to express that memory at a long delay of six weeks after birth. Results revealed that on Days 15 to 16 of gestation, pairing garlic with LiCl in dams did not induce an aversion to garlic in the progeny. However, on days 18 to 19 of gestation, garlic–LiCl pairing induced an aversion to garlic in the progeny, which lasted until after weaning. Following
this, it is possible that at day 15 to 16, the olfactory and gustatory systems are not developed enough to process and perceive the taste stimuli in order to learn a conditioned taste aversion. Thus, long term learning of a CTA may not be possible prior to day 18 of the development of the fetus, revealing that critical development of the olfactory and gustatory systems occurs during this period, which may ultimately be susceptible to modulation and harm in the case of exposure to toxic or potentially teratogenic stimuli.

In conclusion, it has been shown that rats can acquire prenatal taste aversions under the right conditions, and that these aversions can be modulated based on timing, exposure, or sex. For instance, prenatal exposure to drugs such as ethanol, methamphetamines, or ketamine have shown to modulate taste aversions in rats by decreasing or inhibiting acquisition of an aversion as would normally be expected. This may suggest that environmental variables can act to alter the intrauterine environment and lead to significant changes in development, either of the hippocampus in the case of ethanol, or receptors, such as in the case of ketamine, that ultimately lead to behavioral deficits in early childhood, which may extend to adulthood. Additionally, the acquisition of aversions may differ based on the aversive stimulus itself, or based on timeline of acquisition. Results have shown that stimuli will differ in aversive properties, and will therefore differ significantly in their ability to be learned as aversive stimuli in and of themselves, as was the case with milk-borne stimuli. Finally, a timeline of acquisition of prenatal aversions in rats is currently being developed, with results showing that acquisitions are successful beginning around day 18 of gestation, however future studies may further investigate this timeline in order to determine what effect exposure may have earlier in the gestation period, and how that may lead to long-term effects. An investigation of the specificities of the timeline of taste
development is still necessary in order to determine critical windows or periods where these sense systems may be fragile and subject to harmful changes.

**Taste Preferences**

A significant amount of research has also investigated the impact of prenatal environmental stimuli on development of feeding preferences in rats. This research has given further insight into the mechanisms behind which the development of such preferences occur in rat pups, which can, at times, be extended to human models. This section will first examine research evidence for exposure to ethanol ultimately leading to developed preference for the appetitive aspects of ethanol. Additionally, effects of unintentional toxin exposure such as exposure to bisphenol A (BPA) will be examined. Finally, the effect of both protein malnutrition and overeating, or “cafeteria diet,” on subsequent preferences and eating habits in early childhood and adolescence, moving into adulthood, will be examined.

Research involving prenatal exposure to ethanol in rats has allowed for distinct insight on consequences of fetal alcohol exposure. These consequences have been investigated in isolation during the immediate postnatal period and early infancy, as in the case of Arias and Chotro (2005). This study found that pups exposed to ethanol in the prenatal period showed lower levels of activity and higher levels of ethanol intake and behavioral actions associated with eating, such as mouthing and paw licking. Pups exposed to higher doses of ethanol also showed generalization towards sucrose-quinine, an ethanol taste analog in rats. Overall, palatability of ethanol is enhanced in rats exposed in the prenatal period, which leads to heightened preference for ethanol as well as behavioral manifestations of changed neural networks due to exposure to ethanol. Studies have specifically shown that alcohol ingested during the prenatal period can
diffuse into the amniotic fluid and be ingested and sensed by the fetus, whereby the fetus is able to acquire information about ethanol related stimuli and learn about such stimuli.

Additional studies have implicated these consequences to extend beyond infancy and impact adolescence in many different ways. Youngentob and Glendinning (2009) showed that fetal ethanol exposure significantly increased the taste-mediated acceptability of ethanol and bitter taste, but not sucrose in adolescent rats. Increased ethanol acceptability was absent in adult animals, which reveals that effects of fetal exposure are ameliorated by adulthood. This indicates that fetal exposure to ethanol enhances intake by making it taste and smell better. Ethanol is known to reduce the number of trigeminal neurons, which would be expected to reduce the number of channels important for perception of oral irritation. During fetal exposure, rats associate the drug’s reinforcing properties with its chemosensory attributes. Here, it is suggested that prenatal exposure enhances postnatal acceptance through a conditioned response acquired by the chemical and absorptive properties of ethanol.

Alternatively, Glendinning, Simons, Youngentob, and Youngentob (2012) proposed that these changes in eating behavior and specifically development of preference to ethanol may be due to genetic changes that modulate perception of taste stimuli. Ethanol is thought to produce burning sensations in the oral cavity by diffusing into the oral epithelium and stimulating the distal dendritic portions (free nerve endings) of trigeminal sensory neurons in the lingual nerve. It activates the free nerve endings by interacting with the transient receptor-potential vanilloid receptor-1 (TrpV1). Rats exposed to ethanol in the prenatal period licked both ethanol and capsaicin significantly more than control rats when tested in adolescence. Thus, the presence of ethanol in blood or oral cavity during prenatal development leads to a downregulation of TrpV1 receptors, which leads to a reduction of the painful effects caused by both ethanol and capsaicin.
These findings suggest evidence of learning occurring prenatally involving the chemical senses, suggesting that offspring can acquire these preferences prenatally if exposure occurs. These findings suggest that ethanol ultimately leads to preferences due to the specific modulation of the manner in which ethanol and other bitter or painful taste stimuli are processed and perceived by the organism’s senses. Specifically, intrauterine exposure to ethanol leads to a downregulation of free nerve endings, which ultimately reduces the painful sensitivity to these stimuli and therefore leads to increased consumption.

Prenatal or neonatal alcohol exposure has shown to elevate ethanol intake in adolescent rats even when exposure is to doses well below those known to cause neuroteratogenic or morphological defects. One method by which prenatal ethanol exposure may increase ethanol intake is by exaggeration of the normal adolescent insensitivity to the aversive effects of ethanol. This hypothesis was investigated by Gore-Langton and Spear (2019), aiming to determine whether exposure to a moderate dose of ethanol would modulate aversive effects of ethanol if exposure occurs during late gestation. Moderate ethanol exposure during late gestation produced a largely male-specific attenuation to the aversive effects of ethanol during adolescence that later contributes to increases in preference and intake of ethanol. This sex-specific effect could be due to differential susceptibility to ethanol in females compared to males. Specifically, research has shown that males and females process ethanol differently in terms of pharmacokinetics, where when injected with the same ethanol concentration, blood ethanol concentrations peaked fasted in females and reached the nucleus accumbens at a faster rate compared to males (Robinson, Brunner, & Gonzales, 2002).

Ethanol exposure has also shown to alter preference towards other food or drug stimuli. For instance, alcohol consumption and use of tobacco products are highly correlated. There is
evidence that prenatal alcohol exposure affects the central catecholamine receptor systems, the same molecular and cellular targets affected by nicotine. The flavor attributes of both alcohol and nicotine are key contributors to their acceptance. Fetal exposure to alcohol in rats has been shown to increase acceptability in adolescents and decrease normally aversive flavor attributes. Fetal alcohol exposure decreases expression of bitter and oral irritation receptor genes, which modulate alcohol flavor perception in adolescent rats. Mantella and Youngentob (2014) investigated this interaction, finding that alcohol exposure in the prenatal stages in rats reduces aversive response to nicotine in adolescence while having no affect on the appetitive response to sucrose. This occurs by exposure to alcohol decreasing the aversive properties of both the smell and taste of nicotine, suggesting that prenatal exposure to a drug stimulus can alter preference towards an unrelated stimulus.

These prenatal effects of intrauterine stimuli are not limited to drug exposure. In fact, often exposure that occurs unintentionally can be most dangerous. For instance, Xu and colleagues (2011) showed that BPA exposure led to increased preference for sweet taste in males, leading to increased weight gain, higher fat percentage, and increased tail blood pressure. BPA acts to modulate gonadal hormones and therefore leads to changes in the timeline of emergence of sexually dimorphic behavior, specifically reproductive behaviors or behavior indirectly involved in reproduction. These sex-based changes in eating behavior leads to sweet preference in males exposed to BPA in prenatal development, suggesting a critical window in the perinatal period for alteration of eating behaviors based on sexual dimorphic influences. These sex-differences based on BPA exposure may be similar in mechanism to sex differences in response to ethanol and methamphetamine exposure. Specifically, it is quite possible that the developmental timeline of sexually dimorphic behaviors is uniquely affected by external stimuli.
and can ultimately lead to specific differences in males and females in terms of behavior. Due to the fact that all these vital aspects of life are developing at the same time, many variables may be influenced by exposure to outside stimuli that may ultimately become confounding and lead to differences due to influencing each other.

Another significant prenatal disturbance that is commonly modeled in rats is the presence of a hostile intrauterine environment through protein malnourishment or intrauterine growth-restriction. Such research has shown that prenatal exposure to a hostile environment such as protein malnutrition can lead to altered brain function and specifically, anatomy of the hippocampus. Tonkiss, Shukitt-Hale, Formica, Rocco, and Galler (1990) investigated the effects of prenatal malnourishment on altered eating preferences. Results revealed that prenatal protein malnutrition causes increased responding for food on a variable interval in rats as adults. Prenatal protein malnutrition leads to disruption of reward systems, which increases appetitive interest toward not only food reward, but also sweet reward. Malnutrition gives rise to altered appetitive behavior due to the fact that prenatal malnutrition leads to altered reward response systems.

Exposure to adversity in the fetal environment is associated with altered impulsivity in terms of increased preference for sugary foods in both humans and animals. Fetal adversity therefore, contributes to the development of diabetes, cardiovascular disease, and mental health disorders.

Intrauterine growth restriction is associated with increased preference for palatable foods and altered insulin sensitivity. Insulin modulates the central dopaminergic response and changes behavioral responses to reward. Laureano and colleagues (2019) investigated the effects of insulin in intrauterine growth restricted rats on reward pathways. Results showed that food restricted rats ate significantly more palatable foods, and their eating pattern showed significantly higher entropy compared to control rats. Food restricted rats also showed a delayed
dopamine release in response to palatable foods, however, insulin administration reverted this delay. This suggests that fetal adversity alters brain sensitivity to insulin and modulates behavioral responses to palatable foods. Individual differences in dopamine function are associated with increased palatable food consumption in intrauterine growth restricted individuals. Early adversity during gestation, therefore, is associated with development of chronic diseases and obesity later in life, most likely due to the fact that an altered sensitivity to insulin leads to delayed dopamine release, where dopamine cannot properly regulate normal eating behavior.

In the United States, currently, approximately 20% of the population is obese, whereas an additional 30% is considered overweight. Intrauterine growth restricted rats have been used as a model for the programming of obesity in newborns. In one such study, Desai, Gayle, Babu, and Ross (2005) found that at birth, pups of food restricted dams weighed significantly less than pups of normal diet dams. Intrauterine growth restricted offspring in the immediate catch up growth group demonstrated markedly increased weight gain, and exceeded the body weight of control pups. Intrauterine growth restricted pups in the delayed catch up growth group remained significantly below the body weight of controls at three weeks. By nine months of age, intrauterine growth restricted pups in the immediate catch up group were significantly heavier, whereas the other groups were comparable to the controls. These results suggest that offspring obesity may be influenced by prenatal exposure to a hostile environment, which may induce a “catch-up” growth period. In order to prevent and reduce the subsequent development of obesity, the prevention of this catch up growth period may be beneficial. This “catch-up” growth period appears to be due to the generation of a “thrifty metabolism,” which refers to the idea that the organism’s metabolism has adapted to save resources when possible, often through the storage of
fat, in order to prevent death if conditions were to become as they were in the prenatal period, where undernutrition was the norm. Muñoz-Valverde and colleagues (2014) also found that prenatally undernourished rats exhibited low birth weight and accelerated growth, where they reached normal weight by weaning. However, when these pups were overfed during the postnatal period, they showed not only accelerated growth, but also quickly developed increased blood glucose levels and fatty liver. These changes provide additional evidence for a susceptibility to thrifty metabolism, as well as the impressionability of this “catch-up” period, during which external variables can be determinants of later eating behaviors and the development of metabolic disorders throughout life. Ellis and colleagues (2014), suggest that the mechanism and ultimate consequences of this thrifty metabolism is sex-dependent, and fetal undernutrition ultimately programs obesity and insulin resistance. Leptin administration has shown to reverse the metabolic abnormalities shown in offspring of undernourished mothers, but only in females. This study revealed that this difference might be due to sex-dependent differences in hepatic and non-hepatic regulation of leptin levels, where males have shown increased difficulty in modulating the set point back to normal levels.

Conversely, many studies have also investigated the effect of overeating during the prenatal period, specifically examining the possible effects of a high fat or so-called “cafeteria diet” in rats. Obesity and related disorders continue to increase. Appetite regulation is even more challenging due to the availability of “junk foods”, which are defined as heavily processed, highly palatable and hyper-energetic and are often deprived of the vitamins and essential nutrients available in whole unprocessed foods. Bayol, Farrington, and Stickland (2007) showed that rat mothers exposed to a junk-food diet developed a preference for fatty, sugary, and salty foods. Both male and female rat pups exposed to junk food in the prenatal period also showed
increased BMI and body weight compared to other offspring. These results show that a maternal junk food diet during pregnancy and lactation may be an important contributing factor in the development of obesity. This predisposition occurs by a spontaneous preference for fatty, sugary, and salty foods as a result of exposure, which ultimately modulates reward networks, changing overall feeding preferences. Fat diet selection contributors are largely unknown, but a greater consumption of fat is associated with higher caloric intake and increased body weight. To determine whether a high consumption of fat by dams during pregnancy and lactation had an effect on food choice of pups after weaning, Nakashima, Tsukita, and Yokoyama (2008) fed pregnant dams one of three diets: low fat, control, or high fat. Results showed that pups nursed by dams fed the low fat diet had preferential intake for the fat-protein diet compared to pups nursed by dams fed the control diet and the high fat diet. These results suggest that preference for fat taste may be modulated and learned during pregnancy due to exposure to that taste in utero, leading to differential preferential value placed towards that stimulus after weaning. This modulation ultimately leads to differential reward motivations, as shown by Naef and colleagues (2011), where pregnant dams were divided into either a high-fat diet or control diet which continued until weaning. Rat pups exposed to the high-fat diet showed significantly lowered extracellular dopamine levels and reduced D2 receptors in the VTA, which is suggestive of reduced presynaptic D2 autoreceptors specifically in projection areas such as the nucleus accumbens. This suggests that dopamine neurotransmission is unregulated and therefore leads to high concentrations of output dopamine, which leads to modifications in target reward sites such as the nucleus accumbens, ultimately leading to dysregulated reward pathways. This led to rat pups that ate significantly more fat-enriched foods and were significantly more rewarded by fatty foods.
Additional environmental factors other than diet have shown to be influential in shaping preferences and aversions in rats, specifically those occurring after the prenatal period but prior to weaning which may act to affect reward pathways. Neonatal handling, for example, has a profound impact on development and has shown to alter various behaviors, including eating. Neonatally handled rats are more prone to ingest palatable foods on different situations. To evaluate this, Silveira and colleagues (2010) investigated the effect of neonatal handling on incentive value of sweet food in rats using a series of behavioral tests. Results showed that neonatally handled rats showed greater preference for sweet reward and showed higher incentive salience to sweet reward in a runway test. When injected with a dopamine mimetic agent, non-handled rats consumed significantly sweeter food compared to before injection, whereas there was no difference between consumption for handled rats. Repeated once daily handling during the first 10 days of life leads to decreased accumbal dopamine metabolism. Increased dopamine leads to greater ingestion of sweet food in a positive feedback mechanism. Neonatally handled rats eat significantly more sweet food when exposed to it due to the fact that early handling leads to changes in the reward system, leading to higher ingestion but lower hedonic value. Handling during the neonatal period decreases neophobia and leads to a decrease in activity and exploration of novel situations. Neonatally handled rats also exhibit reduced adrenocorticotropic and glucocorticoid responses to stress. Silveira and colleagues (2004) investigated this in order to verify the effect of handling and tactile stimulation during the prenatal period on palatable food ingestion in adult rats. At 15 months of age, handled rats, both male and female, presented a higher intake of sweet reward compared to non-handled rats. Males only from the handling + tactile stimulation group ate significantly more sweet reward, whereas females ate similar amount of pellets to the control group. Neonatal handling leads to an
increased appetite for sweet, palatable food, most likely due to alterations in CNS systems involved in reward, pleasure, feeding, and responses to stress.

Research has proposed that overfeeding during lactation also programs obesity in the adult rat and impacts emotional behavior, an effect that is sex-specific. Wright, Fone, Langley-Evans, and Voigt (2011) explored whether exposure in neonatal rats to cafeteria diet during lactation programmed altered feeding behavior later in life. In normal rats, eating, grooming, and resting, in that order characterize the natural sequence of satiety. This transition from eating to resting is characterized as the onset of satiety. In this study, male rats exposed to the cafeteria diet in the prenatal period showed shorter feeding bouts, with an overall higher frequency of bouts, and latency to rest was delayed. Females exposed to the cafeteria diet also showed increased frequency of eating bouts and spent more time eating, but had no change in latency to rest. These results suggest that manipulations to diet made during lactation, specifically those involving high fat and caloric diets, produce long lasting changes in feeding behavior in rats, both by increasing frequency and duration of feeding. This also suggests that this modulation is sex-specific, again suggesting differences based on sex-specific development, which ultimately presents itself in changed behavior.

In summary, various factors have shown to influence the development of preferences occurring in rats prenatally. Prenatal exposure to ethanol, for example, has shown to modulate the reward pathways and ultimately lead to developmental changes that drive a preference for ethanol due to heightening the appetitive aspects of the stimulus. Similarly to the development of aversions, exposure to external environmental toxins can also lead to significant effects in the development of taste preferences, as is the case with BPA exposure, which ultimately leads to increased sweet preference in males specifically. Finally, the discussion of studies involving both
intrauterine growth restriction due to protein malnutrition and studies which investigated the results of overeating and diets high in fat suggest that the intrauterine environment is vital for developing healthy eating habits and hostile environments can ultimately lead to dysregulated eating behavior that may be influential in driving the development of metabolic disorders and drive the obesity epidemic in our world today. For this reason, future studies should investigate a direct link between metabolic disorders and the intrauterine environment, in order to gain insight on the specific effects that might be driving this connection and how the predisposition for these disorders might be prevented.

**Humans**

*Taste Aversions*

Food aversions and neophobia are a consistent problem among children in infancy, and lead to consistent strife and anxiety among parents. While picky eating and food neophobia are similar, distinctions have been made in the literature and investigation of the etiology of these disturbances in eating behavior. As previously stated, food neophobia largely refers to the tendency to avoid or dislike for trying new or unfamiliar foods, whereas food pickiness and fussiness largely refer to a tendency to refuse certain familiar foods in specific. This section will examine the distinctions between these two distinct types of aversions in infants, providing reasoning behind the distinction between these two aversion types and providing evidence for the possible mechanism behind each.

Smith and colleagues (2017) found that food fussiness and food neophobia were highly correlated, as indicated by high genetic and shared environmental correlations. However, shared environment was shown to play a more significant role in shaping food fussiness when compared to food neophobia. Therefore, home and family environment play a more important role in
shaping food fussiness than food neophobia in early childhood. This is indicated by the fact that food fussiness was more correlated with environmental factors, as compared to food neophobia. Therefore, home environment, family dynamic, and parents diet influence more differences in expression of food fussiness. Similarly, Steinsbekk and colleagues (2017) found that picky eating was more easily modulated by environmental factors, showing that pickiness was moderately stable from preschool to school age, with half of children who displayed pickiness at age four still displaying it at age six. Sensory sensitivity acted as a predictor for pickiness at age six. Parental structuring was found to reduce risk of pickiness in the follow-up, whereas sensitivity increased odds for pickiness. Parental sensitivity and sensory sensitivity both acted as higher predictors for pickiness once children reached school age. These findings suggest that interventions targeting sensory sensitivity and parental styles may aid in altering eating behaviors to provide more nutritional value.

Food neophobia has been shown to be influenced primarily by cognitive factors rather than environmental. Studies such as Kutbi and colleagues (2019) have investigated this distinction, showing that pickiness was positively correlated with three out of five parental strategies, pressure to eat, and parental modeling. Repeated exposure to food was negatively correlated with food pickiness. Disgust and sensory sensitivity were positively correlated with food neophobia. For the most part, social factors mostly influenced presence and maintenance of food pickiness, whereby pickiness was predicted by repeated exposure to food, parental strategies, and peer and parent modeling. Food neophobia, however, was mostly influenced by cognitive factors such as disgust and sensory sensitivity. This suggests that while these eating disorders are interrelated, they are modulated by different processes. Supporting this idea, Galloway and Birch (2003) evaluated a group of seven-year-old girls for traits associated with
food neophobia and pickiness in order to evaluate possible predictors and traits associated with
the two. Results showed that girls with higher food neophobia and pickiness both showed
significantly less vegetable consumption. Overall, pickiness was predicted by environmental
factors such as breastfeeding length, mother’s diet, and home-life, whereas neophobia was
predicted by anxiety, mood, and other dispositional factors.

Similar results suggest that picky eating is likely a combination of child temperament and
parental styles, showing that picky eating increased significantly with age, from one year to five
years (Hafstad, Abebe, Torgersen, & Soest, 2013). Emotionality level and negative affect for
both children and mothers were all associated with an increase in picky eating over time.
Emotional temperament may lead to difficult interactions between parents and children, which
could influence environment surrounding mealtimes, which is ultimately reflected in child’s
dysfunctional eating behavior. These results provide support for the idea that pickiness is
primarily associated with or supported by environmental factors, which drive dysfunctional
eating patterns by negative affect, controlling practices, and hesitancy to encourage varied eating
behaviors in children. Additionally, late introduction of lumpy food was associated with a child
being a very picky eater, along with refusal of solid foods before 6 months, and the child being
fed on demand (Emmett, Hays, & Taylor, 2018). Mother providing fresh fruit and eating the
same meal as the child were protective against later picky eating, whereas feeding ready-
prepared food was predictive of pickiness. Overall, pickiness is predicted by parent’s
unwillingness to introduce new foods and encourage their child to eat a balanced diet. Parents
should be encouraged to introduce lumpy foods before nine months, regularly feed fresh foods,
and to eat the same meals as their children. It is likely that parental guidance of eating modulates
eating behaviors and leads to increased aversive tendencies towards new foods, and in particular, unknown bitter foods such as vegetables.

Conversely, much of the literature has also investigated the idea that food aversions may be modulated by more fixed environmental factors, such as breastfeeding length, rather than other more variable environmental factors such as parental style. For example, Mennella, Daniels, and Reiter (2017) compared aversions of breastfed infants to formula fed infants. Lactating mothers drank vegetable, beet, celery, or carrot juices for one month beginning at 0.5, 1.5 or 2.5 months postpartum or for three months beginning at 0.5 months postpartum. After weaning, infant’s acceptance of carrot flavor and broccoli flavor cereals were assessed. Infants exposed to vegetable tastes showed significantly fewer facial expressions of distaste towards the carrot cereal. Infants exposed to vegetable tastes through their mother’s milk were more accepting of carrot cereal when compared to the control group. These results did not generalize to broccoli flavor, indicating a difference in aversion towards that vegetable taste. Infants exposed most close to postpartum showed significantly more preference towards the vegetable flavors. Infants breastfeed more often during the first few months of life, which may allow them more opportunity to experience the flavors of the vegetables in the mother’s milk for those who were exposed to the vegetable juice just within one month postpartum. For this reason, early life seems to be the optimum time for exposure to taste of diverse and healthier foods. Along with this, Specht, Rohde, Olsen, and Heitmann (2018) showed that infant breastfeeding duration was correlated with vegetable intake and picky eating traits. There was a negative association with duration of exclusive breastfeeding and pickiness, where longer breastfeeding duration revealed lower amounts of picky eating traits. There was a higher intake of vegetables in children breastfed until age six to 10 months when compared to those breastfed for zero to one month.
Results suggest that breastfeeding duration impacts picky eating, whereby children who were breastfed longer showed fewer picky traits. This supports the idea that children who are breastfed longer are exposed to increased diversity of flavors through breast milk. Additionally, children breastfed longer were more likely to have a higher intake of vegetables, which may be facilitated by increased exposure to flavor, increasing palate and decreasing aversion responses to new or bitter foods.

Wild, Jager, Olsen, Costarelli, Boer, and Zeinstra (2018) found that this trend is complicated by cultural influences as well, showing a significant difference in breastfeeding length between three countries, with Danish children being breastfed significantly longer than Dutch or Greek children. Greek children scored higher on vegetable liking than Dutch and Danish children, however, Danish children were less neophobic. A child who had been breastfed for one year ate, on average, 18 grams more vegetables than those who had not been breastfed. Overall, results suggest that there is a link between breastfeeding length and vegetable intake, however this link is not straightforward. Vegetable intake is likely modulated by a conglomeration of factors, such as breastfeeding length, food neophobia, and enjoyment of vegetables.

In opposition of this idea, Barse and colleagues (2017) found no correlation between breastfeeding length and fussy eating. In other words, never breastfed children did not differ significantly from children breastfed for at least 6 months in terms of pickiness. Early introduction of solid foods, however, was correlated with less fussy eating behavior. Results suggest that early introduction of complementary feeding may be preventative against fussy eating, and support the idea that pickiness is primarily influenced by environmental factors such as introduction timing and parental styles. Overall, results suggested that breastfeeding does not
significantly predict or prevent fussy eating. Taken together, these results suggest that pickiness is primarily modulated by environmental factors, which increase exposure to a diverse profile of foods and therefore allow infants to develop preferences for wide variety of foods and decrease their aversions to those foods. While these results may seem to counter results found regarding the benefits of breastfeeding, it is possible that breastfeeding length simply aids in reducing pickiness by increasing exposure to wide variety of tastes, which is only possible if the mother is also consuming varied foods. Therefore, pickiness is likely best prevented or helped by parental encouragement and continued exposure to foods, even when the infant refuses those foods. It is possible that these results are contradictory to other findings due to differences in methodology. Whereas Barse and colleagues (2017) assessed feeding behavior at two, six, and 12 months, and assessed again at four years, Wild and colleagues (2018) measured feeding behavior only one time, when the children were between two and six years of age. It is possible that these differing methodologies led to differing results, in that Barse and colleagues (2017) may have shown a more longitudinal effect of breastfeeding on pickiness and Wild and colleagues (2018) show a more isolated conclusion after breastfeeding has ceased.

Ciborska, Kłobukowski, and Pierzchała (2018) theorized that common aversions in children are due to a combination of factors and influences, which ultimately lead to traditional and cognitive aversions. In their study, Polish children were asked to rank food preference in response to images of food products. A high degree of preference was shown towards sweet foods and fast-food products, whereas a high degree of aversion was shown for indicated fruits and vegetables. Younger children showed the highest rate of rejection and aversions. Interestingly, children showed increased preference for vegetables common to Polish culture compared to other bitter foods. Through this, they determined two types of aversions: traditional
and cognitive. Traditional aversions emerge usually due to a negative experience with a product or dish, such as shown with taste aversions due to sickness or discomfort from the alimentary tract. Cognitive aversions are a more complex process, whereby disliking and rejection of a taste or food group emerges without tasting or experiencing them directly. Preferences and aversions were largely determined by exposure, namely foods and products customary to Polish culture, as well as sweet foods, which offer an evolutionary advantage over sour or bitter foods.

More seriously, aversions in children have also shown to be influenced by external exposure to environmental toxins and drugs during prenatal development. Such research has shown that aversions and the factors that influence them may be more complex than normal pickiness and neophobia during childhood. For instance, Nguyen and colleagues (2018) investigated the effect of toxin exposure during prenatal development. Mothers residing in Vietnam are often exposed to dioxin, a toxin that has been shown to lower cognitive, fine motor, and social emotional skills during development, as well as being associated with reduced growth during the first four months of life. Mothers were interviewed using the Children’s Eating Behavior Questionnaire when infants reached 3 years of age. The Children’s Eating Behavior Questionnaire is an index of children’s eating styles which measures eating behavior on eight scales: food responsiveness, emotional over-eating, enjoyment of food, desire to drink, satiety responsiveness, slowness in eating, emotional under-eating, and food fussiness. Scores are given on a five-point scale, with one representing never and five representing always. Higher scores in the patient report indicate less of a tendency towards those behaviors. Results showed a sex-specific influence of dioxin exposure, whereby prenatal exposure was associated with significantly lower questionnaire scores in girls.
Additionally, issues such as fetal alcohol exposure have shown to be influential in shaping food preferences and aversions. In Werts, Van Calcar, Wargowski, and Smith (2014), children with fetal alcohol spectrum disorder were assessed for eating habits. Half of girls surveyed were obese or overweight, whereas 37 percent of boys showed reduced stature and low weight and BMI for their age range and only 18.2 percent were obese or overweight. All children showed evidence of recurring feeding problems, including reports of constant snacking, lack of satiety, and picky eating. These results may suggest that prenatal alcohol exposure leads to altered self-regulation, leading to a lack of satiety that is associated with altered weight gain and weight distribution over time.

Finally, it is probable that aversions are influenced by more than simply environmental and exposure effects. The role of genetics has been investigated, and shown to play a role in this issue. Namely, Negri and colleagues (2012) investigated the role of bitterness sensitivity in aversions in childhood. Bitterness sensitivity was assessed and genomic DNA from saliva was used to genotype individuals for polymorphisms of the TAS2R38 receptor, a bitter taste receptor that has been shown to modulate most of the variance in human bitter taste. A higher frequency of supertasters was observed among children, even when mothers expressed the same genotype. A higher percentage of supertaster children avoided bitter vegetables or greens altogether compared to adults. Supertaster genotype is associated with increased bitter sensitivity, which is in turn associated with greater levels of food neophobia. Therefore, increased polymorphisms of the TAS2R38 receptor leads to increased bitterness sensitivity, which leads to aversions to traditionally bitter foods, particularly in children, when food neophobia is common during development.
It is likely that pickiness and food aversions in children are a consequence of a variety of factors, which combine cognitive, environmental, and genetic factors to influence these disturbances in eating behaviors. For instance, it is conceivable that bitterness sensitivity through supertasting leads to increased expression of aversions in children, which then leads to parental styles which further shape these aversions and lead to lower consumption of fruits and vegetables which manifests in metabolic disorders due to lack of nutrients and proper intake of diverse foods groups. Nevertheless, it is clear that food neophobia and pickiness have distinct consequences and are represented through differing etiologies. Food neophobia is likely more genetic in influence, where a refusal to try new or unknown foods may be due to specific differences in genetic influence, which may manifest in specific differences in sensation and perception, or cognition. For this reason, the emergence of food neophobia is likely more influenced by prenatal factors that later act to modulate behavior. Conversely, food pickiness seems to be more influenced by environmental factors that occur outside the prenatal period, such as parenting styles and how insistent parents are about providing varied and consistent opportunities to try diverse food groups. In conclusion, these varied mechanisms suggest there is still much to learn in terms of the specific prenatal effects of aversion development in human infants, where further research is necessary to continue to distinguish between specific factors that influence neophobia and pickiness and how the two are distinct.

_Taste Preferences_

Food preferences and altered ingestive behavior have consistently been linked to the presence and development of a host of metabolic disorders that ultimately affect adult life. For this reason, an examination of altered food preferences with respect to the correlates of prenatal and early childhood development are necessary. This section will examine multiple
environmental effects that may modulate and lead to the development of specific taste preferences in utero. Early explorations of possible links to fluid loss and morning sickness to development of salt preference, as well as preferences resulting from exposure to flavors in utero will be examined. Conversely, other results examined suggest that preferences are more intricately linked to childhood diet and mother’s preferences during infancy, rather than during the prenatal period. Finally, an investigation of fetal undernutrition and its effect on later development of metabolic disorders will be assessed.

One of the earliest explorations of the idea that developmental environment and variables affecting that environment may alter food preferences later in life was the idea that prenatal fluid loss may be influential in determining infant salt preference. Twin studies have failed to show an accurate genetic component for this behavior, leading researchers to search for possible environmental components that may predict this preference. Morning sickness is a common occurrence in pregnancy. In fact, nearly two thirds of all women experience nausea or vomiting during gestation (Crystal & Bernstein, 1995). To examine whether morning sickness and increased vomiting can affect postnatal salt preference, Crystal and Bernstein (1995) surveyed participant’s salt use and mother’s vomiting during pregnancy, and asked participants to choose between a variety of snacks varying in sodium levels. Results showed that offspring of women reporting moderate to severe symptoms of vomiting reported a higher level of salt use, when compared to those who reported little to no vomiting. However, there was no relationship between morning sickness ratings and fat or sugar intake by the offspring. Behavioral results showed that when given the choice, morning sickness participants ate twice as much salty snacks compared to non-morning sickness participants. These results indicate a relationship between salt intake and preference based on mother’s experiences of morning sickness during pregnancy.
This may suggest that increased volume depletion or electrolyte loss due to vomiting may be determinant of postnatal salt intake and into adulthood. In a follow up study, Crystal and Bernstein (1998) indicated that this increased preference is present even in infancy, where infants of mothers who experienced moderate to severe vomiting had significantly higher preference for NaCl compared to mothers who experienced none or mild vomiting. Infants of mothers who experienced little to no vomiting showed significantly higher aversive responses to NaCl compared to mothers who experienced moderate to severe vomiting. Results suggest that maternal dehydration, which is induced by moderate to severe sickness during pregnancy, can lead to enhanced salt preference in infants, modulating the amniotic environment and leading to greater salt exposure, which increases familiarity and preference for the mineral. Leshem (1998), indicated that this effect is isolated to salt preference, and revealed that this effect is present cross-culturally. Participants in Israel were tested for preferred concentration of salt and sugar using various methods of avidity, and interviewed for mineralofluid loss during prenatal and infant period. Increased mineral fluid loss in pregnancy and infancy predicted increased preference for salt but not sweet taste. Results suggest that commonly occurring early mineralofluid loss can contribute to salt preference and therefore, a lifetime of increased salt intake. The age range of this study suggests that salt preference extends beyond infancy, and can persist throughout life. These findings suggest that fluid environment during prenatal and infant period can lead to changes in overall preferences and predict food behavior.

Stein, Cowart, and Beauchamp (2006) found that salt preference was further linked to birth weight. At 2 months, acceptance of salt solution was negatively associated with birth weight, whereas birth weight increased, salt intake decreased. Comparable relationships were apparent in a subset of the subjects at three to four years of age. Results suggest that prenatal or
early postnatal events can modulate preference for salt during infancy and childhood, and that these changes can be enduring. Greater sodium intake is associated with higher blood pressure in infants and adults, and because birth weight is inversely associated with blood pressure, this may suggest that salt preference is adaptable for children of lower birth weight as a mechanism for increasing blood pressure to normality.

Similarly, preferences have been shown to develop based on maternal exposure to flavor through the amniotic fluid. During pregnancy, flavors from the mother’s diet can be transmitted through the amniotic fluid and swallowed by the fetus. Because of this, the types of foods ingested by the mother affect the composition of the amniotic fluid, and therefore directly affect the development of taste preferences in the infant prior to exposure to solid foods. To discover whether experience with a flavor in amniotic fluid or breast milk modifies the infants’ acceptance and enjoyment of similarly flavored foods at weaning, pregnant women drank carrot juice only during pregnancy or during pregnancy and lactation (Menella, Jagnow, Beauchamp, 2001). Results demonstrated that infants exposed to flavor of carrots either in amniotic fluid or lactation behaved differently in response to carrot flavor in the solid food base when compared to control infants. Previously exposed infants showed fewer negative facial expressions while feeding with carrot-flavored cereal compared to water-flavored cereal. These results suggest that prenatal and postnatal exposure to a flavor enhances infant’s enjoyment of that flavor. Early flavor experiences in both amniotic fluid and lactation can, therefore, influence food preferences and predispose the infant to favorably respond to a familiar flavor. Hepper, Wells, Dornan, and Lynch (2013), indicated that this effect could produce long-term changes in food preferences over an individual’s lifetime. Mothers were sorted into prenatal garlic exposure group and control group. At eight or nine years old, children were tested for preference between potato
gratin flavored with garlic, and without flavor. Children exposed to garlic during prenatal development ate a greater amount of garlic-flavored potato than children not exposed, both in terms of trial and amount. Results suggested that prenatal experience with a chemosensory stimulus could have an effect on food preferences eight to nine years later. Results showed that children exposed to garlic taste in utero were more likely to eat garlic-flavored foods. This suggests that familiarity with a food in utero allows for modulation of food preferences due to exposure.

Schaal, Marlier, and Soussignan (2000) found similar results suggesting that human fetuses learn odors that they are exposed to through the amniotic fluid. In this study, newborns of mothers exposed to anise flavor were compared to newborns of mothers who were not. Children not exposed to anise flavor in utero exhibited significantly more negative facial responses to the odor compared to infants that were exposed, both on postnatal day one and day four. Overall, infants exposed to the anise flavor in utero showed increased preference for the odor, orienting themselves towards it, whereas infants not exposed showed an aversion to the stimulus, orienting themselves away and displaying negative facial responses. These results suggest that environmental stimuli introduced into the amniotic fluid during late gestation can modulate preferences towards taste and olfactory stimuli. This provides support for the idea that mother’s diet can influence an infant’s taste and odor perception, by mere exposure. Additionally, due to the intrinsic connection between our sense of olfaction and sense of taste, it reasonable that exposure to olfactory stimuli would ultimately produce changes in taste preferences. For instance, Knaapila and colleagues (2017) recently investigated how the pleasantness, familiarity, and identification of spice odors are associated; participants rated the odors of 12 spices for pleasantness and familiarity, and completed a multiple-choice odor identification. Participants
also completed a food neophobia scale. Results suggested that familiar odors were mostly rated as pleasant, whereas unfamiliar odors were rated as neutral or unpleasant. Odor pleasantness was associated with increased consumption of the spice and food neophilia. Results suggest that familiarity and increased exposure to an odor can gradually increase odor pleasantness, and modulate behavioral response towards that odor. Although these effects may not be intrinsically related to developmental changes in food preferences, they allow for insight into the reasons why exposure, either in womb or during infancy, to different foods may lead to more diverse preferences or preferences for specific foods related to exposure.

Recent literature has countered the idea that prenatal exposure to food odors or tastes leads to preferences in infancy and adolescence, and rather have suggested that preferences are more often a result of exposure during childhood and more correlated to maternal preferences. For instance, Ashman, Collins, Hure, Jensen, and Oldmeadow (2016), suggested that diet preferences are more related to mother’s diet after pregnancy than during the prenatal period. To test whether maternal diet during pregnancy and postnatally was associated with child’s diet at two to three years of age, maternal and child diet intake was assessed. Results showed that in terms of fruits and vegetable consumption, maternal postnatal diet was more predictive of higher consumption in children. Maternal diet post-partum, but not during pregnancy, predicted diet quality of children aged two to three. This suggests that quality of mother’s current diet is predictive of the child’s diet, regardless of prenatal exposure. This supports the idea that mothers can act as role models for their children by consuming a wide variety of foods, thereby increasing child’s intake of those foods. This is likely due to a combination of factors, one being increased exposure leading to increased preference for a diverse range of foods. Forestell and Mennella (2007) investigated this, showing that experience is a primary factor in influencing
childhood food preferences. In this study, one group of infants was fed green beans and then the other was fed green beans, followed by peaches for eight consecutive days. Acceptance of both foods was assessed before and after the home exposure period. Results showed that repeated dietary exposure to green beans, with or without peaches, resulted in greater green bean consumption. However, only infants who experienced green beans with peaches displayed fewer negative facial expressions during eating. These results suggest that infants who receive repeated exposure to a food eat more of it and quickly learn to like its flavor over time. However, these results also suggest that while greater ingestion of foods may be related to familiarity, outward expressions of liking may be more related to pairing tastes with both familiar and pleasurable tastes, as in the case of pairing the peaches and green beans. This may contribute to reducing pickiness and food neophobia, and allows for increased preferences of diverse foods. Accordingly, parents should provide infants with repeated opportunities to try diverse kinds of foods, particularly fruits and vegetables, in order to increase consumption of these foods and influence a wide variety of preferences. Parents might also desire to pair unfamiliar or disliked foods with sweet or pleasurable foods in order to reduce outward expressions of disgust and dislike. Skinner, Carruth, Bounds, Ziegler, and Reidy (2002) investigated this effect further, showing that these results occur longitudinally as well. Mother-child pairs were interviewed seven to eight times when children were two to 24 months. During these interviews, mothers reported on child’s dietary intake with respect to food diversity and amount. Pairs were interviewed a second time when the child was six, seven, and eight years old. Results showed that vegetable variety in school-aged children was predicted by mother’s vegetable preferences. Specifically, fruit variety was predicted by breastfeeding duration and early fruit exposure variety. Results suggest that fruit and vegetable variety in school-aged children is primarily
influenced by early food related experiences involving variety of exposure and preferences of parents, and in particular, the mother. This suggests that emphasis should be placed on education of parents to provide a variety of food related experiences in order to increased overall preferences in their children’s diet and increase vegetable and fruit consumption overall, as recommended.

Perhaps one of the primary factors influencing adult preferences that may transition to metabolic disturbances over time occurs in the prenatal exposure to a hostile environment specifically involving famine or growth restriction. Fetal undernutrition has been shown to influence metabolic disorders and hypercholesterolemia by programming metabolism and influencing lifestyle choices. The Dutch Famine was a period of extreme food shortage during the last six months of World War II in the Netherlands. This time period allows for unique studies showing the outcome of fetuses in hostile environments. Lussana and colleagues (2008) found that adults exposed to famine during early gestation were two times more likely to consume a high fat diet, and were less significantly active. These results suggest that adult lifestyle choices may be influenced by prenatal diet and exposure in utero, showing that infants who are exposed to a hostile prenatal environment, particularly involving undernourishment, show increased preferences for high fat food, which leads to a higher atherogenic profile. Similarly, participants in a Brazilian birth cohort were evaluated using a food frequency questionnaire and classified as non, moderately, or severely growth restricted (Babieri, et al, 2009). Results indicated a higher ingestion of carbohydrates in women born with severe intrauterine growth restriction. This led to a diminished consumption of protein. Results persisted even when differences such as socioeconomic status, body mass index, and other lifestyle factors were considered. Results suggest that severe intrauterine growth restriction may lead to a sex-
dependent effect on carbohydrate consumption, whereby carbohydrates preference is observed in women who were exposed to this hostile intrauterine environment. Women are often more prone to eating disturbances, which may explain why this finding was clearer or more evident in women overall. This trend may lead to an increased risk in women exposed to this prenatal environment to develop metabolic or cardiovascular disorders.

In conclusion, a significant link between postnatal diet preferences and exposure to various environmental variables through the amniotic fluid has been found in various studies. Results regarding fluid loss due to maternal sickness suggest that increased fluid loss during the gestational period may not only lead to lower birth weight, but also increased preference for salt, which may ultimately be driven by an adaptive response to increase blood pressure of lower weight fetuses. Additionally, results regarding exposure to specific tastes and food groups during pregnancy suggest a link between familiarity as it occurs in the amniotic fluid and later consumption of those foods in the postnatal period. This may be due to the mere exposure effect, which states that stimuli we are more familiar with will be more preferred. This suggests that the intrauterine environment with respect to exposure to taste may be formative in the eating habits and preferences of a child in infancy. However, results have also suggested that preferences may be primarily driven by maternal food preferences and variety of food groups offered to the child during infancy. Finally, adequate nutrition and the lack of a hostile intrauterine environment appear to be crucial in determining healthy eating patterns across one’s lifetime. Studies examining undernutrition and hostile intrauterine environment reveal significant correlations between these prenatal environments and the development of preferences which drive the development of metabolic disorders later in life. Preference for diets high in sugar and fat may be
due to a mechanism that acts to overcompensate for the hostile environment the fetus was exposed to and drives overeating or increased storage of fat.

**Discussion**

The widespread nature of environmental influences on the prenatal environment make it difficult to pinpoint exact measures by which development of specific systems may be impacted by the intrauterine environment. It is clear, however, that differences exist based on environmental and genetic influences, and that these influences vary in severity and specificity. According to the present research, it is also clear that differences and similarities do exist between the impact on the taste system in terms of preferences and aversions depending on whether you are examining rats or humans.

In rats, aversions are much clearer and specific reasons behind the development of such aversions can be pinpointed due to the specificity of the environmental factors. In rats exposed to ethanol, for example, studies can specifically monitor the effects and reduce variability between the subjects, whereas in human fetuses exposed to such conditions, there is a large amount of variability both in terms of the alcohol exposure and in terms of other environmental variables that may impact development. For this reason, aversions in rats are primarily confined to the development and learning of a conditioned taste aversion in utero, whereas in humans, these aversions can not only surge in the prenatal period, but also be complicated by other environmental factors in the postnatal period, leading to pickiness or neophobia in infants and children. Contrasting these, it is clear that aversions in rats offer a simple explanation as a model for human aversion development, and may be useful in ascertaining the impacts of exposure to various drugs and toxins that cannot be studied directly in human models, but may not be as
useful for determining the etiology of latter eating disturbances that may occur in infancy, such as pickiness and neophobia.

In terms of discerning the development of preferences and the impact this may have later on in adult life, it seems to be clear that environmental exposure to various foods or toxins have an effect on the development of preferential eating behaviors in both rats and humans. In rats, research seems to show that a hostile intrauterine environment which either lacks proper nutrients or has an overabundance of fatty and high caloric foods eventually leads to an altered reward state, whereby the fetus adapts to either go through a “catch-up” phase or tends to prefer high calorie foods due to exposure. This altered reward state can eventually lead to the development of obesity and generation of other metabolic diseases in adulthood. This is very similar to what occurs in human fetuses exposed to a hostile environment, as often evidenced by the Dutch Famine cohort. However, preferences in humans has also shown to involve more complex mechanisms, where evidence of long term learning of stimuli exposed during gestation leads to development of preferences due to increased exposure and familiarity to these stimuli. While this occurs in rats as well, it is clear that, at least for the first few years of infancy and postnatal life, the prenatal environment is crucial in shaping a child’s eating behavior in terms of what is eaten and not eaten. Additionally, conversely to rats, human models of preferences have shown a unique and crucial impact of parental style and exposure during the postnatal learning period as well. The types of foods a child is exposed to in infancy, as well as how persistent parents are in delivering various types of food to the child, are huge determinants of the kinds of foods that child will prefer and eat more of during their entire lifetime. This impact of postnatal learning has shown up more clearly in human models, where rats are not necessarily as impacted by exposure or parental styles after the prenatal period.
Additionally, clear links can be made between weaning studies in rats and studies that examined the role of breastfeeding in postnatal feeding behaviors both in terms of preferences and aversions. In rats, weaning studies suggest a role of not only the prenatal period, but also the pre-weaning period in the prevention or development of aversions and preferences. Specifically, the development of aversions is limited to stimuli that are not milk-borne, as adaptively, pups seem to be protected from the development of these types of aversions due to the necessity of that stimulus for survival. However, rat studies have not extensively shown a role of pre-weaning diet on later preferences and aversions. In humans, significant connections have been made between breastfeeding and food choices later in infancy and even adulthood. Maternal diet during breastfeeding and lactation appears to be just as predictive of later preferences and aversions as the prenatal environment. Many studies have suggested that maternal diet and preferences during this period allow for exposure through lactation that leads to further familiarity and increased preference towards these familiar tastes.

Breastfeeding has been implicated in humans as determining in the development of both preferences and aversions. Primarily, breastfeeding length seems to be determinant in forming preferences and aversions due to the fact that as breastfeeding length increases, the opportunity to be exposed to diversified food groups increases. For this reason, infants that are breastfeed for a longer period of time and more often show fewer aversions and increased preferences for diverse foods. Conversely, infants that were not adequately breastfed, or were not exposed to diverse food groups through this period seem to develop more aversions and ultimately lead to eating disturbances. For this reason, many aversion studies implicated breastfeeding in the development of aversions, whereas preference studies implicated breastfeeding in preference development as well. This relationship could require further research and explanation in order to
understand the specific variables and situations that lead to aversion susceptibility and those that lead to preferences, as well as how robust those developments may be. Research may indicate a timeline or specific variables that may account for these differences, also investigating the line between healthy preferences and aversions and those that may interfere with daily eating behaviors and ultimately lead to disease.

The role of reward and the modulation of the reward system appear to play a significant role in eating behaviors, both in terms of aversions and preferences, in both rats and humans. In rats, aversion studies implicate the role of reward in terms of methamphetamine exposure, which ultimately leads to dysregulated reward systems. However, similar effects were shown in preference studies, specifically those involving prenatal undernourishment and protein malnutrition that ultimately leads to altered insulin sensitivity and dopaminergic response, altering response to sweet reward and promoting the development of metabolic disease. Very similar results occur in human studies, where reward is implicated in a dysregulated reward system in studies involving fetal thrifty metabolism and catch up growth. Additionally, studies involving neonatal handling implicate the role of reward and the pleasure pathway directly by showing that touch and proper care are necessary for the normal development of the reward system, which ultimately manifests in changes in eating behavior when dysregulated. Overall, reward and dopaminergic response have been implicated in the development of all types of abnormal eating behaviors. Ultimately, it seems that a healthy reward system is the driving force in the proper development of aversions and preferences, and may be the primary investigation for future studies desiring to understand more about not only the consequences of abnormal development of eating behaviors, but also the specific neural correlates and mechanisms behind why these abnormalities occur.
Overall, it appears in utero exposure to any kind of stimulus, whether negative or positive, seems to have a distinct impact on development in both rats and humans. For instance, in rats, exposure to harmful stimuli such as ethanol or other drugs can lead to significant changes in neurological development that ultimately manifest themselves in behavioral changes that impact daily life. Additionally, in utero exposure to high fat diet or protein malnourishment leads to programming that can ultimately lead to overeating or increased storage of fat later in life. This is similar to studies involving exposure to these variables in humans, where undernourishment or high fat diet can lead to very similar results. However, human studies involving in utero exposure to tastes and varied food groups provide insight that rat studies cannot, due to the fact that these studies can be longitudinal and observe long-term effects of varied exposure versus limited exposure, specifically observing changes in behavior that may be reported either by the parents or the child themselves. Overall, though there are differences in in utero exposure between rat studies and human studies, it appears that in both these cases, stimuli from the external environment are able to uniquely affect development during the prenatal period by crossing to the amniotic fluid and ultimately influencing perception, neurological, and behavioral development. This reveals that though studies between these diverse groups may ultimately differ, there are significant correlations and connections that can be made in studies that utilize rat models for in utero exposure, allowing us to learn more about potential dangers during prenatal development, which may then be qualified by more longitudinal and behavioral results in humans.

Future research is necessary to fully ascertain the mechanisms behind which exposure and familiarity increases preference for a specific food group, exploring how that exposure, both in utero and postnatal, can impact adult life and ultimately lead to disease. Research may also
focus on practical ways to influence parenting styles in order to maximize exposure and preference for varied food groups, specifically increasing vegetable and fruit consumption. Additional research using rat models may be necessary in order to fully understand how exposure in utero can impact development, as well as ascertain how salient these stimuli are in the amniotic fluid.

In conclusion, prenatal exposure to various types of stimuli, related to food or not, can impact development of the taste system directly, or lead to changes that may lead to learning that ultimately affects food choices. These alterations in development patterns occur both in human and non-human animals, and can significantly impact not only prenatal life and infancy, but also eating behavior in adulthood. This can lead to a pattern of disordered eating behavior, which can ultimately impact several generations.
References


probable link to overweight and obesity. *Neurotoxicology and Teratology*, 33(4), 458-463.