# Abstract

Motivation:

* Human studies indicate that alcohol exposure during gestation not only increases the chance for alcohol abuse during the vulnerable period of adolescence, but also nicotine dependence. The younger the first experience, the higher the chance of continuing abuse.
* The flavor and odor (aversive odor, bitter taste and oral irritation) attributes of both alcohol and nicotine can be important determinants of their initial acceptance.
* epigenetic chemosensory mechanisms: fetal alcohol exposure increases adolescent alcohol acceptance, in part, by decreasing the aversion to alcohol’s bitter and oral irritation qualities and its odor.
* Co-morbid dependence: the incidence of smoking among alcoholics as compared to non-alcoholics is quite high, Increases in alcohol and tobacco use showed a monotonic relationship during adolescence and through young adulthood, possible reasons include
  + socio-cultural factors
  + shared genetic influences
  + neurobiological factors: pharma- cologic cross-tolerance
  + the underlying mechanism is essentially unknown
  + the central catecholamine receptor systems: prenatal alcohol exposure impacts many of the same molecular and cellular targets influenced by nicotine
    - Nicotine and alcohol both stimulate the mesocorticolimbic dopamine system and this, in turn, promotes intake and reinforcement [21].
  + alcohol interacts with nicotinic cholinergic receptors
  + with enhanced alcohol avidity, contribute to the observed link with smoking behavior
* Are there potential mechanisms by which prior fetal alcohol exposure could directly impact initial choice and intake behavior for both drugs? key contributing factors include:
  + flavor
    - epigenetic chemosensory mechanism: a mother’s use of alcohol during pregnancy is potentially transmitted to her children
      * Nicotine has several component chemosensory qualities in common with alcohol
    - orosensory mediated behavioral findings:
      * T2r- and Trpm5- expressing solitary chemosensory cells in the nasal cavity also respond to nicotine
      * fetal alcohol exposure has also been shown to decrease the expression of bitter (T2rs: in particular, those sensing quinine) and oral irritation (in particular, Trpv1) receptor genes
      * decreased expression of Trpm5, a receptor important to calcium channel opening during the transduction of bitter, sweet and umami
      * decreased the expression of T2r38, a bitter receptor that responds to phenylthiocarbamide [PTC] and 6-n-propylthiouracil [PROP] and one that has been implicated in human alcohol and nicotine acceptance.
  + Odor
    - fetal alcohol exposure alters the expression of genes important for synaptic transmission, plasticity and neuronal development in the olfactory bulbs of adolescent animals
    - the observation of decreased T2r, Trpv1 and Trpm5 gene expression in the oral cavity may likely generalize to the nasal cavity where both Trpv1 (nasal trigeminal: e.g., [42,43]) and, solitary chemosensory cells expressing T2r and Trpm5 [44–46] respond to inhaled irritants

Purpose:

* Given that alcohol and nicotine have noteworthy chemosensory qualities in common, we investigated whether fetal exposure to alcohol increased the acceptability of nicotine’s odor and taste in adolescent rats
* tested whether fetal alcohol exposure altered the (a) odorant-induced innate behavioral response to nicotine odor and (b) orosensory-mediated acceptability of nicotine

Approach:

* Study rats were alcohol-exposed during fetal development via the dams’ liquid diet. Control animals received ad lib access to an iso-caloric, iso-nutritive diet throughout gestation.
* Animals were tested between postnatal (P) day 28 and 35
  + These ages were chosen because previous studies demonstrated a decreased aversion to the component qualities of odor, bitter and oral irritation that persisted into adolescence
  + given that nicotine shares the same aversive qualities as alcohol and smoking is co- morbidly expressed with alcohol consumption in humans, these ages permitted us to test the hypothesis that prenatal alcohol experience would alter the postnatal behavioral response to nicotine in adolescence
  + ET: alcohol exposed dams
    - Female rats with similar biological traits received an ad-lib liquid diet that provided 35% of their daily calories via alcohol during G11–20, subsequent to gradual exposure to lower concentrations of the diet beginning on G6
  + FCL: free-choice liquid animal
    - maltose dextrin was substituted for the calories provided by alcohol
* Odorant-induced innate behavioral responses to nicotine odor (Experiment 1)
  + 20 ET and 20 FCL chosen (half male and half female)
  + whole-body plethysmography was used to monitor the inherent sniffing responses (i.e., respiratory airflow patterns) following the delivery of air or 5 different concentrations of the odorant nicotine
  + The nicotine concentration series was 3.125\*10-3 , 6.25\*10-3, 1.25\*10-2, 2.5\*10-2 and 5\*10-2 . For each concentration of odorant, an animal received 20 trials of the randomized presentation of 10 air and 10 odorant stimuli
  + The airflow patterns generated by the animals’ innate sniffing responses to odorant were initially broken down by computer evaluation of the patterns into 14 different respiratory measures
  + In the first step of creating an ‘‘Index’’ we used a standard principle component analysis (PCA), the animals’ 14\*5 data matrices were compressed to a set of 2-PCA factors\*5-concentration matrices
  + separate analyses were performed on each PCA factor, using multivariate linear regression (five concentrations of nicotine served as the dependent variables and gestational exposure as the independent variable)
  + Each of the regression analyses, in turn, provided the coefficients for each concentration of nicotine for the respective PCA factors.
  + The derived index value from each PCA factor for a given animal was the total of the regression constant from the analysis plus the individual PCA value at each concentration of nicotine multiplied by the applicable coefficient. This resulted in x and y pairs of data that were used to place each rat in a nicotine odorant stimulus, behavioral response space.
* orosensory-mediated responses (taste responsiveness) to nicotine solutions (Experiment 2) were obtained, using whole-body plethysmography and brief access lick tests
  + 22 ET and 22 FLC chosen
  + Evaluated the taste responsiveness of ET and FCL animals to nicotine and the appetitive tastant sucrose
  + Experiment subjects received 10 days of training (each session lasts 30 minutes) before the experiment to learn to drink from sipper tube, prior to training, the rats were deprived of water for 22.5 hr to encourage licking
  + the rats participated in a single 30-min test session for a concentration series of sucrose (0.03, 0.1, 0.2, 0.3, 0.6 M) and nicotine (0.1, 0.3, 1.0, 3.0, 6.0 mM) on different days. DI water was also included as a stimulus in each session. The two testing days were separated by a recovery day where food and water were provided
  + order of presentation pseudo-randomized using a balanced Latin Square design
  + the average number of licks and latency to first lick to each stimulus concentration across the entire test session was determined

Result:

* Experiment 1
  + there was a separation between ET and FCL, suggesting a degree of difference in maternal alcohol treatment on the inborn behavioral response to nicotine odor.
  + a significance test (two-tailed t: P,0.05) was accomplished using the combined weighted city-block distance of the effect sizes for the two indexes which demonstrated that an overall significant consequence of prenatal alcohol exposure on the innate odor- mediated behavioral response to nicotine (t [18] = 2.38; P,0.03).
  + Multivariate analysis of variance (MAN- OVA) showed no evidence for either source of variation (F [2,25] = 1.32, P.0.2 and (F [2,25] = 1.47, P.0.2).
* Experiment 2
  + there was no evidence (t [42] = 20.64, P.0.5) of a differential effect of maternal treatment on the number of stimulus presentation blocks completed
  + For the nicotine testing, only 19 ET and 19 FCL animals contributed to the data set. Six animals were eliminated because of unstable responding across stimulus presentations. On average, there was no evidence (t [36] = 21.08, P.0.2) of a differential effect of maternal treatment on the number of stimulus presentation blocks completed
  + With respect to nicotine, animals in both treatment groups showed a parallel non-linear concentration-dependent decrease in the average number of licks with increasing concentration that was relatively flat between 0.1 to 1 mM nicotine and then decreased sharply thereafter. Nonetheless, there were obvious effects of maternal treatment.
  + Because of the non-linear relationship among all pairs of the dependent variables (especially nicotine) the natural log transformed lick data were used to evaluate the main effect of ET vs. FCL maternal treatment (a between factor) and concentration
  + For nicotine, there was a significant effect of both prenatal treatment and concentration
  + For sucrose, there was significant evidence of an overall effect of concentration There was no evidence of an effect of prenatal exposure
  + Figure 3 illustrates the response latency of adolescent rats as a function of maternal treatment for the nicotine and sucrose concentrations. the latency to respond to each stimulus concentration of nicotine was, on average, faster in the ET animals
  + For sucrose, although there was evidence for an average effect of concentration on the animals’ response latencies, there was no evidence of an effect of treatment
* Compared to controls, rats exposed to fetal alcohol showed an enhanced nicotine odor response that was paralleled by increased oral acceptability of nicotine, not altering the response to sucrose solution.
* Given the common aversive component qualities imbued in the flavor profiles of both drugs, our findings demonstrate that like postnatal alcohol avidity, fetal alcohol exposure also influences nicotine acceptance, at a minimum, by decreasing the aversion of both its smell and taste.
* behavioral consequence of fetal alcohol exposure occurred because of the maternal treatment effect at the level of the orosensory periphery through a decreased expression of T2r and Trp receptor genes central to the transduction of alcohol’s bitter and oral irritating qualities, respectively, as well as the sensory transduction of bitter (more specifically, Trpm5).
* Alcohol and nicotine have common chemosensory attributes, these are received and conveyed through the same receptors and pathways, we hypothesized that fetal alcohol exposure would alter the: (1) odorant-induced innate behavioral response to nicotine odor and (2) orosensory-mediated acceptability of nicotine in adolescent rats. The present study found that fetal alcohol exposure from G6-G21 yielded an altered odor-mediated response that we interpret as either a reduced aversive or an enhanced preference response to nicotine that was paralleled by increased oral acceptability of nicotine in adolescent animals
* Moreover, they highlight potential chemosensory-based mechanism(s) by which fetal alcohol exposure increases the later initial risk for nicotine use, thereby contributing to the co-morbid expression with enhanced alcohol avidity.

Challenges:

* The relationship should not be overstated, partly because that both alcohol and tobacco products are, at a minimum, the earliest potentially addictive substances used. Alcohol and tobacco product use are also so called ‘‘gateway drugs’’ that precede the subsequent use and abuse of illicit substances
* the mechanism(s) that specifically tie prenatal alcohol exposure to both postnatal alcohol and nicotine dependence still remains largely an open question, a number of mechanisms may be involved

Limitations:

* Used rats as subject of experiment
* the plethysmography data does not directly assign a valence to the observed alterations in sniffing. It only identifies whether a main effect of treatment has occurred.
* the shorter latency to respond to nicotine solutions could be interpreted as an additional index of either an enhanced nicotine oral acceptability, odor preference or both. At present we cannot distinguish between these potential alternatives.

Contributions:

* Where common chemosensory mechanisms are at play, our results suggest broader implications related to the consequence of fetal exposure with one substance of abuse and initial acceptability of others. This is important as many licit and illicit drugs have prominent chemosensory components with likely common underling sensory transduction pathways.
* The data extend upon prior fetal alcohol work by providing a broader perspective for the proposal that a mother’s drug use can be passed to their children via experience-based chemosensory mechanisms
* They also speak to a broader concern regarding the association between maternal drug use and postnatal vulnerability to co-morbid choice behavior, as many licit and illicit drugs have prominent chemosensory components.
* the intersection between the effects of fetal alcohol exposure on specific chemosensory related receptor expression and the extent to which specific inhaled odors stimulate olfactory, trigeminal and solitary chemosensory cells of the nasal cavity likely impacts the observed odorant specificity of the behavioral response