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| **Effect of Prenatal Nicotine Exposure and Serotonin deficiency on arousal to hypoxia in rat pups** |
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| **Introduction** Smoking during pregnancy increases the risk for SIDS and 70% of SIDS infants have a deficiency in brainstem serotonin (5HT). Arousal in response to hypoxia may be impaired by repeated exposures to hypoxia, a phenomenon called “habituation”. We hypothesized that prenatal nicotine exposure (PNE) with or without a 5HT deficiency progressively impair arousal during successive bouts of hypoxia in the pups.  **Material and Methods** Dams were fed either a control (C) or a tryptophan deficient (TD) diet, associated with a 41-56% decrease in medullary 5HT. From E4 to P10, a subcutaneously implanted osmotic pump continuously delivered either normal saline (NS) or nicotine (NIC) (6mg/kg/day) corresponding to about 0.5-1 pack of cigarettes a day in human smokers. We used a mixed model to determine the influence of DIET (C, TD), DRUG (NS, NIC), AGE (P7, P14) and TRIAL (1-4) on arousal latency. P7 and P13 rat pups from each litter were exposed to 4 successive bouts of 10% oxygen and the time to arousal (latency) from the onset of hypoxia was determined behaviorally. Blood cotinine measurements confirmed that nicotine continued to be present in the blood until P13.  **Results** The results showed a main effect for DIET (P=0.025), DRUG (P=0.011) and TRIAL (P<0.001).  Although there was no main effect of AGE, there were interactions between AGE and TRIAL (P<0.001) and AGE, DRUG and TRIAL (P=0.024). Overall, the TD diet had only a small effect on arousal, whereas prenatal NIC exposure prolonged arousal latency independent of DIET.  With both the C and TD diet the effect of NIC on arousal was more prominent at P13, where arousal latency was significantly greater in the NIC pups by trials 3 and 4.  In contrast, at P7, arousal latency was longer in the NIC pups only during the first trial of hypoxia and habituation was abolished. The TD diet resulted only in a slight shortening of arousal latency that was not influenced by prenatal NIC.  We also evaluated heart rate variability (HRV) from the ECG to evaluate any effects of PNE on the autonomic control of heart rate.  The mean heart rate and the standard deviation of HR were higher at P13 compared to P7, as expected.   Measures of short term variability, mostly accounted for by respiratory sinus arrhythmia (RSA), including the RMSSD and the SD1 of constructed Poincare plots revealed lower RMSSD (P=0.013) and SD1 (P=0.013) in NIC pups at P13.  There was no accompanying effect of PNE on the LF/HF ratio.  **Conclusions** These experiments show that pups exposed to nicotine in utero and possibly during the early postnatal period (via milk) have impaired arousal in response to repeated episodes of hypoxia, and decreases in HRV similar to those reported in SIDS infants.  We speculate that smoking during pregnancy impairs arousal and autonomic function and that these alterations increase the risk for sudden death when faced with a potential life threatening stressors. NIH PO1 HD36379 |
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