ENCYCLOPEDIA
on Early Childhood
Development

Prenatal Stress and Offspring Development in Nonhuman Primates

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January 2011, Éd. rév.

Introduction

Psychosocial stress during pregnancy has been linked to adverse developmental outcomes in children, including low birthweight and shorter gestation duration, reduced neonatal attention and habituation to stimuli, and increased risk for Attention Deficit Hyperactivity Disorder, schizophrenia, speech impairments and social abnormalities.[1-6] Primate studies conducted under controlled laboratory conditions have provided an inferential link between rodent studies and human epidemiological studies.

Subject

Increased stress and violence in everyday life has resulted in a growing concern about the effects of maternal stress on child outcomes. This is particularly true in the economically underprivileged sector of our society, where individuals are more likely to be subjected to uncontrollable daily pressures and more serious stressors such as relocation and unemployment. Because women under stress are more likely to smoke cigarettes, consume alcohol, and engage in other stress-

related behaviours, there is often a clustering of negative events, which can compound the adverse effects on the developmental outcome of their children.

Problems

It is difficult to establish causal links between prenatal stress and developmental outcomes in human studies due to selection bias and possible confounding variables. Even with statistical corrections, it is impossible to ascertain whether major confounders have been eliminated or whether the method of adjustment has effectively removed confounders. In primate studies, one can use randomized experiments, inferring causal connections between prenatal stress on one hand, and offspring behaviour and development on the other. Nonhuman primate studies make an excellent model for studying prenatal stress because of the similarity in brain structure and biological processes of stress reactions to humans between nonhuman primates and humans. Other factors include the richness of nonhuman primate social organization and their complex cognitive capabilities, the opportunity to isolate prenatal stress from other factors and to employ a standard stress treatment, and the ability to investigate possible biological underpinnings.[7-9] The disadvantages of nonhuman primate studies are that it is necessary to use small sample sizes, cost is high compared to rodent studies, and one must still generalize from animals to humans, albeit this inferential leap is smaller with nonhuman primates than it is with rodents.

Research Context

Stressful events stimulate the release of stress hormones, which can cross the primate placenta (at least in small amounts), and can influence fetal development. Studies with rodents and with nonhuman primates have demonstrated that when dams were injected with a stress hormone (corticotrophin-releasing hormone) (CRH), or when pregnant rhesus monkeys were injected with adrenocorticotrophic hormone (ACTH), their offspring showed effects similar to those observed in prenatally stressed offspring.[10,11]

Key Research Questions

Our research used daily exposure to three short bursts of noise (115 dB sound at 1 m, 1300 Hz) as a prenatal stressor to answer the following questions:

- Does unpredictable daily psychological stress during pregnancy have an adverse effect on birthweight, gestation duration, neonatal neurobehaviour and/or stress reactivity?

- Is there a sensitive period or time of enhanced vulnerability for prenatal stress effects?
- Are maternal stress hormones an important part of the mechanism for the prenatal stress effects on the offspring?
- Does prenatal stress interact with other potential negative events, such as fetal alcohol exposure?
- Is there continuity between effects observed during infancy and later cognitive functions?
- Does prenatal stress have long-term effects on dopamine system function as assessed with *positron emission tomography (PET)* imaging?

Recent Research Results

- Prenatal stress significantly reduced birthweight, but did not shorten gestation durations, although all birthweights were within the range of what is considered normal for rhesus monkeys.[12] Prenatal stress was also associated with a neurobehavioural profile that included reduced neonatal attention, motor maturity and motor activity.[13-15,10] When exposed to stressful events, prenatally stressed monkeys showed more disturbance behaviour and higher levels of stress hormones, compared to controls.[16-18,12]
- The effects of prenatal stress on birthweight and early neurobehaviour appear to peak during early gestation and taper off during mid-to-late gestation.[14]
- Maternal endocrine activation was shown to be one of the underlying mechanisms for the effect, since administering ACTH to pregnant females resulted in effects similar to those observed in prenatally stressed monkeys.[10]
- When prenatal stress was combined with fetal alcohol exposure, the most adverse effects on birthweight and behaviour were observed, compared to controls.[19-21]
- There was a significant association between reduced neonatal attention and learning deficits during adolescence in nonmatch-to-sample, showing some continuity between early deficits and later outcomes.[20]
- Prenatally-stressed and prenatal stress + prenatal alcohol-exposed monkeys showed two differences in dopamine function compared to monkeys that were not exposed to prenatal stress: 1) higher ratio of *dopamine D2 receptor* binding to dopamine (DA) synthesis in the striatum.[22] Less dopamine is synthesized and the receptors increase or up-regulate to

compensate, and 2) higher dopamine transporter binding which regulates extracellular levels of dopamine in the *striatum*.

Conclusions

Nonhuman primate studies, conducted under carefully-controlled laboratory conditions, are an important link between rodent research and human studies. Primate studies indicate that prenatal stress induced lower birthweights, reduced early attention and motor maturity, slower learning, impaired emotion regulation and induced long-term changes in dopaminergic function in the striatum. It is interesting to note that adolescents and adults with ADHD show a 40-50% increase in dopamine transporter binding in the striatum, however not all studies have found this effect. Early gestation appears to be a period of enhanced vulnerability for some of these effects, although effects are also observed from chronic stress during mid-to-late gestation. More research is needed to study the severity of stress, chronicity versus single episodes of stress, timing of stressful events, and the effects of clustering of negative events. In people, coping strategies are very important in ameliorating the impact of stress, and such strategies cannot be studied in animals. Research to date supports a tentative conclusion that there is a causal connection between prenatal stress and developmental outcomes in humans and nonhuman primates.

Implications

Because development is shaped by a highly complex process involving the interplay of biological and environmental factors,[23] it is reasonable to add prenatal stress to the list of risk factors that may adversely affect development, especially when combined with other risk factors. Relevant public policy issues in this area of research include the identification and reduction of existing risk factors and the enhancement of available protective factors in pregnant women. The public needs to be educated about risk factors during pregnancy, including prenatal stress, and the clustering of negative events. Professional training for service providers should include information relevant to risk factors, including stress, and the possible effects on offspring.

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