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SESSION IV - THE CNS AS A TARGET FOR ENDOCRINE DISRUPTORS AND OTHER POLLUTANTS

BENZO[a]PYRENE AFFECTS DEVELOPMENT AND FUNCTION OF HUMAN GNRH NEUROBLASTS

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The increasing environmental pollution represents a major concern not only for the global ecosystem, but also for human health. Endocrine disrupting chemicals (EDCs), such as benzo[a]pyrene (BaP), are widespread pollutants that can interfere with the endocrine system, altering reproductive function and embryo development. However, little is known about BaP effects on human reproductive axis at central level. The central regulatory network of the reproductive system is mediated by gonadotropin-releasing hormone (GnRH) neurons, which originate in the olfactory placode and, during fetal development, migrate into the hypothalamus. We investigated the direct effects of BaP on development of GnRH-secreting neurons taking advantage of a primary culture isolated from the human fetal hypothalamus (hfHypo). hfHypo cells express the enzymes cytochrome P450 (CYP1A1 and 1B1), required for metabolic activation of BaP and that expression was strongly induced by Bap exposure (0.2 and 10 μM for 24 h). Moreover, treating hfHypo with BaP (10 μM, 24 h) increased reactive oxygen species (ROS) production and influenced the total antioxidant capacity of the cells. From a functional point of view, BaP exposure (10 μM, 24 h) significantly reduced both mRNA and protein expression of GnRH and decreased the mRNA level of the receptor for kisspeptin (KISS1R), the main physiological regulator of GnRH neuron function. In addition, since the migratory process is a crucial event for the correct maturation and functionality of GnRH neurons, we investigated the effect of BaP on pre-migratory GnRH neuroblasts isolated from the human fetal olfactory epithelium (FNC-B4). Preliminary results, using a transwell assay, indicated that BaP pre-incubation (10 μM for 24 h) significantly reduced FNC-B4 migratory properties. In conclusion, our findings demonstrate that BaP may directly affect GnRH neuron maturation and function by altering migration process and interfering with GnRH and KISS1R expression, suggesting a possible mechanism underlying EDCs-related alterations of reproductive function.

EFFECTS OF CHRONIC EXPOSURE TO BISPHENOL-A IN PREGNANT FEMALE MICE

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Bisphenol A (BPA), an organic synthetic compound found in some plastics and epoxy resins, is one of the best known and most studied EDCs (Endocrine Disrupting Chemicals, *i.e.* an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action). Exposure to BPA is especially dangerous if it occurs during specific "critical periods" of life, such as intrauterine, perinatal, juvenile or puberty periods, when organisms are more sensitive to hormonal changes. This exposure can originate, in adulthood, both physiological and behavioural alterations. In particular, we focused on the effects of exposure to BPA during pregnancy, which represents a particularly sensitive period not only for the fetus but also for the mother. In this study we treated C57BL/6 dams orally with a dose of 4 μg/kg body weight/day (*i.e.* EFSA Tolerable Daily Intake dose) of BPA dissolved in corn oil (N=11) or with vehicle (N=8), starting with mating and continuing for 20 weeks. We monitored the dams, evaluating their body weight (daily) and food intake (once a week). During the last two weeks of treatment we followed up the estrous cycle and we performed the Three-Chamber Test to assess sociability. We did not notice differences in body weight, food intake, number of pups and female-to-male ratio in the litters, but we found that BPA-treated dams tend to have higher pup mortality and to develop an aggressive behavior towards males during mating. In addition, BPA-treated dams showed an altered estrous cycle, spending more time in estrus compared to the controls. The Three-Chamber Test revealed that the male-preference of the control mice, measured as time spent within the chamber of the male non-tester mouse, was lost in BPA-treated females. Therefore, we decided to analyze vasopressin and oxytocin systems, measuring both fractional area and number of cells, in paraventricular, supraoptic and suprachiasmatic nuclei of these animals. Although we did not find any alteration in the oxytocin system, we did observe some alterations in the vasopressin system, which could be partially linked to the behavioral alterations. These results suggest that exposure to BPA may pose a risk even in adulthood (given the long-term exposure period, the persistence of these compounds in the environment and the ability of bisphenols to accumulate in certain compartments of the body), particularly when it occurs during delicate periods such as pregnancy.