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163.14 / WW22 - Sexually dimorphic effects of early postnatal genistein administration on kisspeptin system

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Abstract
Genistein (GEN), a phytoestrogen contained in soy and other legumes, may interfere with the endocrine system in multiple ways. Therefore, it may induce permanent alterations of estrogen sensitive circuits as the Kisspeptin system. In rodents, this system is clustered in two hypothalamic populations located within the rostral periventricular area of the third ventricle (RP3V) and the Arcuate nucleus (ARC), and it regulates both the timing of pubertal onset and estrous cycle. Kisspeptin neurons project primarily to the GnRH neurons, but also in a few other locations, including the Paraventricual nucleus (PVN), the most important center for the regulation of food intake and energy expenditure. We analyzed the effects of the early postnatal treatment (from PND1 to PND8) of CD1 pups of both sexes with GEN (50 mg/kg body weight dissolved in sesame oil) or with the vehicle (control, CON) on the Kisspeptin system and other physiological parameters of 2 month-old mice. Kisspeptin was revealed by immunohistochemistry (antibody AC#566, Tours, France), and quantified (Image J) by calculating the Fractional Area (FA) covered by the immunoreactivity (in PVN, RP3V and ARC), and the positive cell number (in RP3V). Early postnatal exposure to GEN, in a dose comparable to the exposure level in babies fed with soy based formulas, induced sexually dimorphic effects. While GEN treated males showed only a minor decrease of testicles' weight, probably related to the significant decrease of testosterone's concentration we measured in feces ($P<0,001$), the treatment affected multiple parameters in females. GEN treatment induced an advanced pubertal onset in females (premature vaginal opening) and altered the development of reproductive system (increased urogenital distance and increased uterus' weight). In addition, GEN females showed an increased weight and an altered estrous cycle. Kisspeptin immunoreactivity was significantly reduced in adult GEN females compared to CON females (FA, RP3V, $P<0,01$; ARC, $P<0,001$; PVN, $P<0,001$; cell number, RP3V, $P<0,001$), whereas no changes were observed in males. In conclusion, the early postnatal exposure of CD1 mice to GEN determines long-term sex specific effects on the Kisspeptin system, female pubertal timing, fertility and metabolism.