Opposing dose-related effects of neonatal BPA exposure on female pubertal timing and neuroendocrine control

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We recently reported that neonatal exposure of female rats to 1 or 10 µg/kg.day of diethylstilbestrol could respectively cause late or early puberty and consistent changes in maturation of pulsatile GnRH secretion. Endocrine disrupting effects of low bisphenol A (BPA) doses in the µg range are a matter of controversy. We studied the effects of neonatal exposure to a very low dose of 25 ng/kg.day in comparison with 5mg/kg.day. Newborn female rats were exposed to vehicle (corn oil) or BPA injected subcutaneously from postnatal day 1 (PND 1) to 5 or from PND 1 to 15. The rats were followed for vaginal opening (VO) and estrous cyclicity. The GnRH interpulse interval that was known to decrease between PND 10 and 25 was studied *ex vivo* using hypothalamic explants obtained at PND 15, 20 or 25. Gene expression in the retrochiasmatic hypothalamus was assessed by whole exome RNA-sequencing on PND 20 (3 samples per condition). After neonatal exposure to 25 ng/kg.day of BPA for 15 days, the age at VO was delayed (35.3 ± 0.7 days vs 33.5 ± 0.5 days in controls) while advancement (32.1 ± 0.6 days) was observed using 5 mg/kg.day. The difference in pubertal timing between the two doses was significant. The late VO after exposure to 25 ng/kg.day of BPA was preceded by a significant increase in GnRH interpulse interval (52.5 ± 0.8 min vs 44.6 ± 0.7 min in controls) at PND 20. By contrast, early VO after exposure to 5 mg/kg/d was preceded by a significant decrease in GnRH interpulse interval (40.3 ± 0.1 min vs 42.8 ± 0.4 min). Similar dose-related changes in GnRH secretion were observed after BPA exposure from PND 1 to 5. At PND 20, after exposure from PND 1 to 15, RNA expression of 10 genes showed significant opposing changes in the high vs low BPA dose groups. Fourteen genes displayed an expression that was only affected by 25 ng/kg of BPA. The dose of 5 mg/kg resulted in modified expression level of 472 genes versus controls. A significant difference in level of RNA expression was observed for 1407 genes when comparing the two BPA dose conditions. In conclusion, neonatal exposure to a very low dose of BPA was followed by a delay in pubertal timing with consistent changes in pulsatile GnRH secretion. Changed hypothalamic RNA expression confirmed the effects of the two BPA doses with opposing changes of similar genes in relation to BPA dose and alteration of distinct genes by each of the two doses.