Bisphenol S chronic exposure interacted with ewe metabolic status to impair female reproduction

Marie-Emilie Lebachelier de la Riviere, Alice Desmarchais, Ophélie Teteau, Virginie Maillard, Svetlana Uzbekova, Sébastien Elis

Animal Reproduction

X INTERNATIONAL SYMPOSIUM ON ANIMAL BIOLOGY OF REPRODUCTION (ISABR)

FEMALE REPRODUCTIVE BIOLOGY

Bisphenol S chronic exposure interacted with ewe metabolic status to impair female reproduction

Lebachelier de la Riviere ME., Desmarchais A., Téteau O., Maillard V., Uzbekova S., Elis S.

INRAE, CNRS, Université de Tours, PRC, 37380, Nouzilly, France

Bisphenol A (BPA), a plasticizer used in the food industry, is reported to be an estrogenomimetic endocrine disruptor, involved in deleterious effects on oocyte meiosis and maturation as well as in steroigegenesis impairment. BPA being regulated, structural analogs emerged including bisphenol S (BPS). Studies on fish and rodent species reported that BPS affects reproduction similarly to BPA. Moreover, because metabolism affects the ovarian functionning, we hypothesized that the metabolic status could interact with the effects of environmental factors. Therefore, this study assessed BPS chronic effects at dose corresponding to the tolerable daily intake defined for the BPA, on oocyte quality, steroidogenesis and granulosa cell proteomic data. Groups of 20 ewes were subjected to either a restricted (R) or well-fed (WF) diet and to a bisphenol daily exposure (0, 4 or 50 µg/kg/day) for more than 3 months, thus generating 6 groups : R0, R4, R50, WF0, WF4 and WF50. After hormonal oestrus synchronization and ovarian stimulation, oocytes were surgically recovered (OPU sessions) and underwent *in vitro* maturation (IVM), fecundation and development. Developmental rates were analyzed at day 2 and 7 after IVM. At the time of slaughter, after 5 month of daily exposure to bisphenol, After hormonal oestrus synchronization, the follicular fluid and granulosa cells of the preovulotary follicle were collected. The follicular fluid underwent a steroidomic analysis while the granulosa cells underwent a proteomic analysis. Body weight was higher in well-fed compared to restricted ewes at the time of oocyte punctures (diet effect, $p<0.0001$, 64.3 ± 1.2 kg vs 54.1 ± 1.2 kg, respectively) which was also the case for body condition score (diet effect, $p<0.0001$, 2.92 ± 0.02 vs 2.18 ± 0.02, respectively). Regarding embryo production data, the most interesting finding was a significant diet x BPS dose interaction that was reported for cleaved embryos, >4-cell embryos, blastocyst and early blastocyst numbers. Moreover, steroidomic analysis of the preovulatory follicle showed a significant interaction between metabolic status and BPS exposure for seven steroids, including estradiol. Indeed, while exposure to BPS impaired estradiol concentrations in follicular fluid of well-fed ewes, this was not reported in restricted ewes. Granulosa cell proteomic analysis of the preovulatory follicle confirmed the interaction between metabolic status and BPS exposure as most of the proteins corresponding to the diet effect (21 and 30 proteins) differ depending on the BPS exposure. Lastly, among the proteins that varied after BPS exposure, the most interesting one is the beta-glucuronidase. Bisphenols, with oestrogenic properties, are metabolized into glucuronide bisphenols, without glucuronide properties. Nevertheless, the beta-glucuronidase has been reported to be able to remove the glucuronide part of BPA glucuronide and therefore to turn it back into BPA with oestrogenic properties. This protein that is expressed at the follicular level, is also overabundant after BPS exposure and could therefore prolonged the BPS effects at the ovarian level. Moreover, according to both the literature and our data, the beta-glucuronidase expression increases with adiposity. To conclude, our data highlighted the deleterious effects of BPS and its interaction with the metabolic status, indicating that its use in food packaging should be regulated. Our data also suggested that individuals with higher adiposity might be more sensitive to bisphenols effects.