

Sex-dependent physiological consequences of perinatal bisphenol A exposure in seasonal Djungarian hamsters

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ARTICLE INFO

Edited by Bing Yan

Keywords:

Bisphenol A
Reproduction
Energy metabolism
Perinatal exposure
Seasonality

ABSTRACT

Bisphenol A (BPA) has been identified as a substance of very high concern regarding its effects on the reproductive and metabolic health of human and wildlife. However, the impacts of early-life BPA exposure on the mammalian reproductive and metabolic adaptations to seasonal changes have never been addressed. We investigated the effects of perinatal BPA exposure on the fertility and maternal behaviour of the seasonal Djungarian hamster, as well as growth, puberty onset, and the ability of male and female offspring to adapt to seasonal changes later in life. Female Djungarian hamsters maintained under a long photoperiod (16 h light/8 h dark) were orally exposed to 5 µg/kg of body weight/day of BPA, or vehicle, during breeding, gestation, and lactation. BPA-treated female hamsters had a higher number of living offspring despite providing less maternal care, as compared to untreated females. Male and female offspring exposed perinatally to BPA exhibited an enhanced growth after weaning, along with reduced (in females) or normal (in males) food intake, but no modification in pubertal onset. When adult, females exposed perinatally to BPA exhibited a reduction of ovarian atretic follicles, whereas perinatally BPA-exposed males showed unaffected morphometric testicular parameters. Further, BPA-exposed females displayed a deficit in energy expenditure when compared to unexposed females. When transferred to a short photoperiod, BPA-exposed females, but not males, exhibited an accelerated integration of the short photoperiod phenotype, with faster reproductive quiescence and a larger decrease in body weight, food intake, and glycemia. Overall, this study reveals that perinatal BPA exposure in Djungarian hamsters alters maternal behaviour, offspring postnatal survival growth, and energy expenditure, and later in life reproductive and metabolic adaptations to seasonal change, with major sex differences.

1. Introduction

Anthropogenic and natural chemicals with endocrine activities, known as endocrine-disrupting chemicals (EDCs), are ubiquitously released into terrestrial and aquatic environments, leading to widespread exposure of both humans and wildlife. Numerous field and laboratory-based studies have reported that EDCs could impair the reproduction of invertebrates, fish, amphibians, reptiles, birds, and mammals, with populational, individual, tissular, cellular and molecular level-impacts (Birnbaum, 2013; Kumar and Holt, 2014; Marlatt et al., 2022).

Most studies investigating the impact of EDCs on wildlife and animal reproduction have focused on traditional reproductive endpoints, such as fertility, sperm quality, reproductive tract development, ovulation capacities, and circulating sex hormone levels (Kumar and Holt, 2014; Marlatt et al., 2022; Tubbs and McDonough, 2018), without considering

the potential effects of EDCs on the seasonal nature of reproduction (Moralia et al., 2022). In moderate to high latitude zones of the world, most animals use a seasonal reproductive strategy to ensure that offspring are born at the optimal time of the year when environmental resources are abundant, thereby securing species survival (Bronson, 1985; Shinomiya et al., 2014). Consequently, their reproductive events follow a seasonal calendar dependent on robust annual changes in day length, known as the photoperiod (Nakane and Yoshimura, 2019). Because reproduction is a high-energy function that cannot occur when energy supplies are low, the timing of gestation and birth is functionally matched with seasonal cycles of energy metabolism. A striking example is the transition toward a state of reproductive quiescence, along with decreased food intake and body weight, increased catabolised fat reserves, and spontaneous daily torpor observed in the Djungarian hamster (*Phodopus sungorus*) to save energy during winter (Ebling, 2020).

It is now well established that seasonal cycles of reproduction and

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growth are synchronised with annual photoperiodic changes through a central photoneuroendocrine system conserved among taxa (Dardente and Simonneaux, 2022; Hazlerigg and Simonneaux, 2015 for reviews). In mammals, photoperiodic cues are translated into the production of the pineal hormone melatonin, whose nocturnal secretion lasts longer during winter nights (short photoperiod, SP) compared to summer nights (long photoperiod, LP). Melatonin acts on thyrotroph cells in the *pars tuberalis* of the pituitary gland to regulate TSH secretion, which in turn regulates the expression of deiodinases, enzymes that control the metabolism of thyroid hormones, in tanycytes located along the third ventricle of the hypothalamus. Seasonal variations in hypothalamic triiodothyronine (T3) concentrations subsequently synchronize the expression of neuropeptides involved in controlling the hypothalamic-pituitary-gonadal and metabolic axes, thus orchestrating reproduction and energy balance according to the season.

In a recent pioneering study, we have reported that the neuroendocrine control of seasonal functions in adult Djungarian hamsters is impacted by environmental exposure to bisphenol A (BPA) (Moralia et al., 2025). BPA is a plasticizer massively used in the production of polycarbonate plastics and epoxy resins, found in many commonly used consumer products. BPA is continuously released into the environment, leading to constant exposure for both humans (Vandenberg et al., 2007) and wildlife (Nehring et al., 2017; Corrales et al., 2015; Markman et al., 2007; Gonkowski et al., 2023). We found that the oral exposure of adult male and female Djungarian hamsters to various doses of BPA (5–500 µg/kg of body weight/day (µg/kg/d)) alters the dynamics of their reproductive and metabolic photoperiodic adaptation, as well as the expression of hypothalamic seasonal genes with major sex differences (Moralia et al., 2025). However, EDCs exposure also occurs during early life periods known as critical windows of sensitivity (Colborn et al., 1993). Notably, developmental exposure to BPA not only induces immediate effects on reproductive and metabolic development but also shows persistent alterations of the adult reproductive and metabolic axes by acting on the organization of neuroendocrine control systems (Lopez-Rodriguez et al., 2021; Mackay et al., 2013; Tudurí et al., 2018). In this context, we have investigated whether early-life exposure to BPA in Djungarian hamsters could alter their developmental and seasonal physiology. Female Djungarian hamsters were thus exposed orally to either the vehicle (control) or BPA at 5 µg/kg/d, from breeding until postnatal day 15. Maternal fertility and behaviour were assessed, and pups were monitored for growth and timing of puberty onset. In adulthood, general physiological parameters and hormone levels were characterised. Finally, part of the F1 generation was transferred from LP to SP for 12 weeks, during which further physiological parameters were monitored, including body weight, food intake, pelage changes, and reproductive status.

2. Material and methods

2.1. Animals

The study involved breeding male and female Djungarian hamsters, on average 4-month-old, born and raised in the Chronobiotron animal facility (UMS 3415, Strasbourg, France). The breeding process included two sessions with a 7-day cohabitation between a male and a female, to ensure an adequate number of pups for the experiments. Hamsters were maintained in type II L cages at a temperature of $22 \pm 1^\circ\text{C}$ under LP conditions (16 h light/8 h dark) with food and water provided *ad libitum*, and enriched with nest cottons, wooden sticks, and a stainless-steel tunnel. Pups were weaned on the 28th postnatal day and placed in individual enriched type II L cages. To minimize environmental chemical contamination, precautions outlined in Moralia et al. (2025) were followed. Breeding hamsters and their pups were fed with a low phytoestrogen breeding diet (SAFE 150), and weaned pups were fed with a low phytoestrogen maintenance diet (7011 P, Altromin International). All animal experiments were conducted in accordance with ethical

guidelines and were approved by a local committee on animal experimentation (CREMEAS), adhering to the regulations of the French Ministry of Higher Education and Scientific Research (authorization #22595–2019102317455140v5).

2.2. BPA exposure and experimental design

Female hamsters were exposed to the vehicle or BPA from the first day of breeding until the 15th postnatal day, as offspring start to eat pellets and drink less mother's milk after the first two postnatal weeks (Fig. 1A). Each female received a 200 mg piece of jelly daily, containing either 0.05 % ethanol (for control animals, as the solvent/vehicle for BPA) or BPA (Sigma Aldrich, #239658) adjusted to a dose of 5 µg/kg/d. A daily check confirmed that hamsters fully eat their jelly ration within 10 min. Briefly, jelly batches were prepared every 5 days by heat-dissolving agar-agar in water with breeding diet powder (1 g per 100 ml). The solution was allowed to cool down, and ethanol or BPA was added before gelling. The volumes of BPA or ethanol added to the solution were adjusted based on the average body weight of the females in each experimental group. As the quantification of BPA contamination in wild rodents is unknown, the selection of the dosage range was based on the human tolerable daily intake (TDI) of BPA, set at 4 µg/kg/day by the European Food Safety Authority (European Food Safety Authority, 2015) (experiments being performed between 2021 and 2022, before the establishment of the 2023 TDI), and from few data available in terrestrial wildlife (Gewurtz et al., 2021; Markman et al., 2007). To validate internal exposure doses, the primary metabolite of BPA, BPA-glucuronide, was measured using LC-MS/MS (see *Plasma assays* section for method details) in plasma of 10 BPA-fed and vehicle-fed female hamsters. Blood samples were collected 1 h after the final oral ingestion of the jelly. This timeframe was chosen based on a preliminary study showing that BPA-glucuronide achieves peak plasma concentrations 1 h after jelly ingestion. Significant concentrations of BPA-glucuronide were found in the plasma of 9 of the 10 females exposed to BPA (with a mean value of 8.9 pmol/ml plasma, corresponding to approximately 3.6 ng/ml, which is compatible with BPA found in the plasma of European starlings in Canada (Gewurtz et al., 2021), while no trace of the metabolite was detected in the females exposed to the vehicle (Fig. 1B).

Two cohorts (from three breeding families in our animal facility) comprising a total of 60 breeding pairs were generated. Each female of the breeding pairs was fed either 5 µg BPA/kg/d ($n = 27$) or vehicle ($n = 33$), with weekly weight adjustments. As BPA-treated females tended to be more fertile, they were more BPA-exposed pups than control pups, the number of offspring per group for follow-up experiments was balanced by selecting litters in a way that ensured equal representation from the three breeding families in our colony, maintaining comparable genetic backgrounds across treatment groups. Both cohorts were monitored for maternal behaviour from PND 2 to PND 14, and for the weekly body weight and food intake of the pups after weaning (PND 28) until they were 6 months old. At this age, cohort 1 (8 females and 9 males perinatally exposed to BPA, and 8 females and 8 males exposed to vehicle) was assessed for its ability to adapt metabolism and reproduction to a short photoperiod (SP, 8 h light/16 h dark) over 12 weeks, when blood and tissue were sampled for further analyses. Cohort 2 (7 females and 12 males perinatally exposed to BPA, and 8 females and 8 males exposed to vehicle) was dedicated to monitoring puberty onset and assessing metabolic and reproductive adult status through indirect calorimetry, as well as tissue and blood sampling (Fig. 1A).

2.3. Longitudinal monitoring of reproductive and metabolic physiology

Gestation and birth. Breeding females were weighed weekly until gestation, with care taken to reduce handling-induced stress during this period. Birth onset was checked twice a day starting from the 15th day of

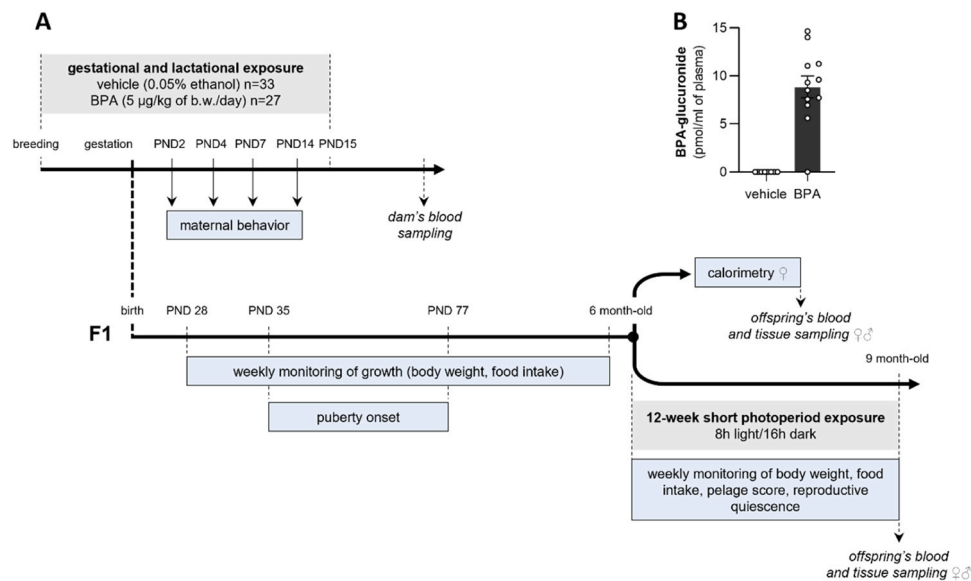


Fig. 1. Experimental design. (A) Female Djungarian hamsters were fed daily with a jelly containing 5 µg bisphenol A (BPA)/kg body weight ($n = 27$) or vehicle (0.05 % ethanol) ($n = 33$) from the first breeding day to offspring's 15th postnatal day (PND 15). Maternal behaviour was evaluated at PND 2, 4, 7 and 14 (arrows). Offspring (F1)'s metabolic and reproductive somato-endocrine parameters were monitored from PND 28 to adulthood (6 months). At this point, male and female hamsters exposed to BPA or vehicle during the perinatal period were divided into two groups: one group was exposed to a short photoperiod for 12 weeks, during which modifications of their metabolic and reproductive parameters were monitored; another group was assessed for energy expenditure through indirect calorimetry (only females) and for reproductive status by tissue and blood sampling. (B) At the end of the exposure period, BPA-glucuronide levels were measured in the plasma of BPA-exposed ($n = 10$) and vehicle-exposed ($n = 10$) dams. b.w., body weight.

breeding. Various fertility parameters were assessed, including pregnancy rate, litter size, sex ratio, and pup mortality rate.

Maternal behaviour. A scan sampling method was employed to score maternal behaviour after pups' birth (Catanese, Vandenberg, 2016; Franks et al., 2011; Palanza et al., 2002). Two 60-minute scoring sessions were conducted daily at PND 2, 4, 7, and 14, one hour after and one hour before the lights were switched on and off, respectively. The maternal behaviour of each dam was scored at 3-minute intervals, resulting in 21 observations per session and 42 observations per day for each dam. Maternal behaviours were categorised as caring behaviours (nursing, licking/grooming pups, nest-building) and non-caring/out-of-nest behaviours (self-grooming, eating, drinking, no contact with pups).

Growth and puberty onset. After weaning (PND 28), pups' body weight and food intake were measured weekly. Onset of vaginal opening (VO) in females and balano-preputial separation (BPS) and estimated testicular volume (ETV) in males were evaluated weekly between the 5th and the 11th postnatal week to define the timing of puberty (Butler et al., 2007). In females, puberty onset was defined as the first week following a consecutive two-week period of VO observations. Left testis ETV (mm^3) was calculated as $(\text{testis width})^2 \times (\text{testis length})$, both measured with callipers under light isoflurane anaesthesia. The onset of male puberty was defined as an ETV threshold of 100 mm^3 and the presence of complete BPS. Previous studies have correlated an $\text{ETV} > 100 \text{ mm}^3$ with specific criteria indicating functional spermatogenesis, including testis pair weight $> 300 \text{ mg}$ and detectable circulating testosterone concentrations (Butler et al., 2007; Schlatt et al., 1995).

Energy homeostasis. 6-month-old females exposed perinatally to BPA ($n = 8$) or vehicle ($n = 8$) were analysed for energy expenditure, respiratory quotient (RQ), and locomotor activity using an indirect calorimetry system (Phenomaster, TSE Systems). In each metabolic cage, air was sampled at 25-minute intervals over a 72-hour period (with the first 6 h of recording excluded due to habituation), with gas sensors determining O_2 consumption, CO_2 production, and RQ. Feeding sensors weighed food, and a photobeam break counting system recorded hamster movement in the X- and Y-axes, allowing quantification of locomotor activity. Hamsters were weighed immediately before recording,

and this body weight value was used as a covariate in subsequent statistical analyses using the online analysis tool CalR (version 1.3, Mina et al., 2018). Measurements were averaged by hour and then by daily period (day and night phases).

Short photoperiod phenotype. 6-month-old hamsters exposed to BPA ($n = 8$ females and $n = 9$ males) or vehicle ($n = 8$ female and $n = 8$ males) during gestation and lactation were transferred to SP (8 h light/16 h dark) for 12 weeks. According to the exclusion criteria previously defined in Moralia et al. (2025), one male in the control group was categorised as a photo non-responder and excluded from the analyses. Body weight and food intake were monitored weekly from SP transfer. The pelage change, ranging from 1 for brown summer fur to 5 for white winter fur (Figala et al., 1973), was scored weekly from the 6th to the 12th week of SP. The time of transition to the winter coat was determined when the hamsters displayed a stage > 2 . Reproductive quiescence was monitored weekly from SP transfer by observing the closure of the vaginal orifice in females, the resorption of the BPS and the reduction in ETV in males. The time of reproductive quiescence was defined as the week in which the vagina remained closed for at least 3 consecutive weeks in females, and as the week in which the $\text{ETV} < 100 \text{ mm}^3$ in males.

2.4. Tissue and blood sampling, histology, and hormonal assays

All the male and female hamsters, exposed to BPA or vehicle during the gestation and lactation periods and kept constantly in LP or transferred to SP for 12 weeks, were killed at 7–9 months of age, 4 h after lights on. Anaesthesia, intra-cardiac perfusion, and blood sampling were carried out according to the methods described in Moralia et al. (2025).

Reproductive organ histology. Gonads were dissected, weighed, and fixed in Bouin's solution for 48 h before being dehydrated in ethanol baths and stored in butanol until paraffin embedding. Histological studies of ovaries (Figure S1) and testes (Figure S2) were conducted using classical paraffin section method and hematoxylin and eosin staining for either ovarian follicle counting or testis morphometric analysis. The paraffin-embedded gonads were cut into 5 (ovary) or 6 (testis) μm -thin sections, and serial ribbons containing 3–5 sections were

collected every 100 μm of tissue and mounted on gelatin-coated microscope slides. The tissues were processed through deparaffinization in toluene, rehydration through a graded series of ethanol baths, and staining with hematoxylin and eosin following the protocol outlined by Mark et al. (2007). The number of follicles of different stages, based on the classification established by Moffatt-Blue et al. (2006) for the Djungarian hamster, was counted in selected ovary sections observed using an optical microscope (Olympus BX41). Only follicles with a visible oocyte were counted to prevent double-counting. Counting followed the order in which serial sections were mounted. For each corpus luteum, its location, morphology, and progression across consecutive slices were monitored to track it through the series and avoid multiple-counting in adjacent sections. For each testis, spermatogenic epithelium area and ratio were assessed by morphometric analyses performed on whole slides scanned at 40x magnification with the Nanozoomer 2.0 HT (Hamamatsu) using the program NDP.scan. Based on Sziva et al. (2022), the average diameter and the average lumen diameter of 30 random cross-sections of seminiferous tubules (ST), as round-shaped as possible, were calculated using the NDP.view software (version 2.9.29). The area of each ST and the lumen of the ST were manually selected to calculate the spermatogenic epithelium area ratio using the following calculations: spermatogenic epithelium (μm^2) area = ST area (μm^2) – lumen area (μm^2), and spermatogenic epithelium area ratio (%) = (spermatogenic epithelium area (μm^2)/ST area (μm^2)) $\times 100$. The lengths of four different points of the spermatogenic epithelium were measured and averaged to obtain the thickness of the spermatogenic epithelium.

Plasma assays. Circulating concentrations of BPA-glucuronide in dams and testosterone in male hamsters were measured using LC-MS/MS, following the procedure described in Moralia et al. (2025). Estradiol concentrations were measured in 50 μl plasma from female hamsters using the Estradiol ELISA Kit (#501890, Cayman Chemical), after extraction in methanol. Intra- and inter-assay variations were < 5 %, and the kit displayed a sensitivity of 20 pg/ml.

2.5. Statistical analyses

All data are presented as the mean $\pm$ SEM of n animals and were analysed using GraphPad Prism 8.0.2 (GraphPad Software Inc, San Diego, USA), Python, CalR (version 1.3, Mina et al., 2018) for data obtained in metabolic cages, or R (version 4.4.1) for the principal component analysis (PCA). For all statistical analyses, the significance level was set at a P -value < 0.05. For each statistical analysis, the normality assumption was checked using the Shapiro-Wilk test, and the homogeneity of variance assumption was evaluated with a homoscedasticity plot, determining the use of parametric or non-parametric statistical tests accordingly. Proportions and frequencies were compared between experimental groups using χ^2 tests. Repeated values over time were analysed between experimental groups using a two-factor analysis of variance (ANOVA) followed by *post hoc* Sidak tests. Mixed-effects analyses were employed instead of two-factor ANOVA when values were missing. Comparisons between experimental groups were analysed by *t*-tests or Wilcoxon-Mann-Whitney tests.

Metabolic parameters independent of body weight (RQ, ambulatory activity) were analysed using one-factor ANOVA. Period-averaged values (diurnal, nocturnal) of body weight-dependent metabolic parameters (food intake, energy expenditure, O_2 consumption, CO_2 production) were correlated with body weight, which was utilised as a covariate in a generalised linear model (GLM). If the model indicated no interaction between the group and body weight, the metabolic parameter was compared between experimental groups by analysis of covariance (ANCOVA). If the model showed a significant interaction effect between the group and body weight, the metabolic parameter was compared between experimental groups by ANOVA with interaction (or ANCOVA for non-parallel slopes). For the PCA, the MissMDA package in

R was used to impute the incomplete datasets, and the final PCA was performed with the FactoMineR package.

3. Results

3.1. Fertility and maternal behaviour of female hamsters exposed to BPA

Females exposed to BPA tended to have higher pregnancy rates than those exposed to the vehicle ($p = 0.165$), with 44.4 % of mated females exposed to BPA carrying a pregnancy to term, compared to only 27.3 % of females exposed to the vehicle (Table 1). The number of pups per litter was similar in both BPA- and vehicle- exposed dams. However, BPA-exposed females experienced significantly fewer pup losses (3.3 %) than the females exposed to the vehicle (26.2 %), with 2 out of 9 (22.2 %) controlled dams having lost their entire litters, whereas this did not happen in BPA-exposed dams. As a result, at PND28, the number of pups was almost 2 times higher in BPA-exposed than in vehicle-exposed dams. Exposure to BPA did not affect the sex-ratio of the litters.

Spontaneous maternal behaviour (from PND 2–14) was predominantly directed towards the pups on both exposed groups (Fig. 2). However, BPA-exposed dams exhibited a significantly reduced frequency of pup-directed care behaviours, and consequently a significantly higher frequency of non-pup-directed behaviours, compared to vehicle-exposed females at PND14, but not earlier (Fig. 2A). Further analysis of specific behaviours on that day showed that BPA-exposed dams tended to spend less time nursing their pups ($p = 0.09$) and more time eating ($p = 0.14$, Fig. 2B).

3.2. Effects of gestational and lactational exposure to BPA on metabolic and reproductive parameters of F1 Djungarian hamsters

Various somatic and endocrine parameters were monitored throughout the life cycle of male and female hamsters born from BPA-exposed or vehicle-exposed dams to assess the impact of BPA exposure on the offspring's growth and puberty and their energy metabolism and reproductive system at adulthood. Both male and female hamsters were monitored to reveal putative sex-dependent effect of perinatal exposure to BPA.

In female hamsters, despite similar body weights at weaning (Fig. 3A), those exposed to BPA perinatally gained more weight (74 % $\pm$ 6 %) than those exposed to vehicle (51 % $\pm$ 4 %) from postnatal week 4 (weaning) to 22 (Fig. 3B, C). By contrast, BPA-exposed females showed significantly reduced cumulative food intake during the same post-weaning period compared to vehicle-exposed females (Fig. 3D). In order to understand this unexpected association of an increased body

Table 1

Pregnancy and litter data collected from dams exposed to vehicle (0.05 % ethanol) or BPA (5 $\mu\text{g}/\text{kg}/\text{day}$). BPA, bisphenol A; PND, postnatal day; **: $p < 0.01$; ***: $p < 0.001$.

	Vehicle (n = 33 breeding pairs)	BPA (n = 27 breeding pairs)	Statistical significance (p-value)
Percentage of pregnancy	27.3	44.4	0.165
Total number of pups per litter at birth (mean $\pm$ SEM)	4.7 $\pm$ 0.4	4.9 $\pm$ 0.5	0.69
Percentage of dead pups at PND 28	26.2	3.3	0.0007 ***
Percentage of females which lost the entire litter	22.2	0	0.086
Total number of live pups at PND 28	31	57	0.0056 **
Sex-ratio at PND 28 (mean $\pm$ SEM)	0.50 $\pm$ 0.02	0.55 $\pm$ 0.08	0.574

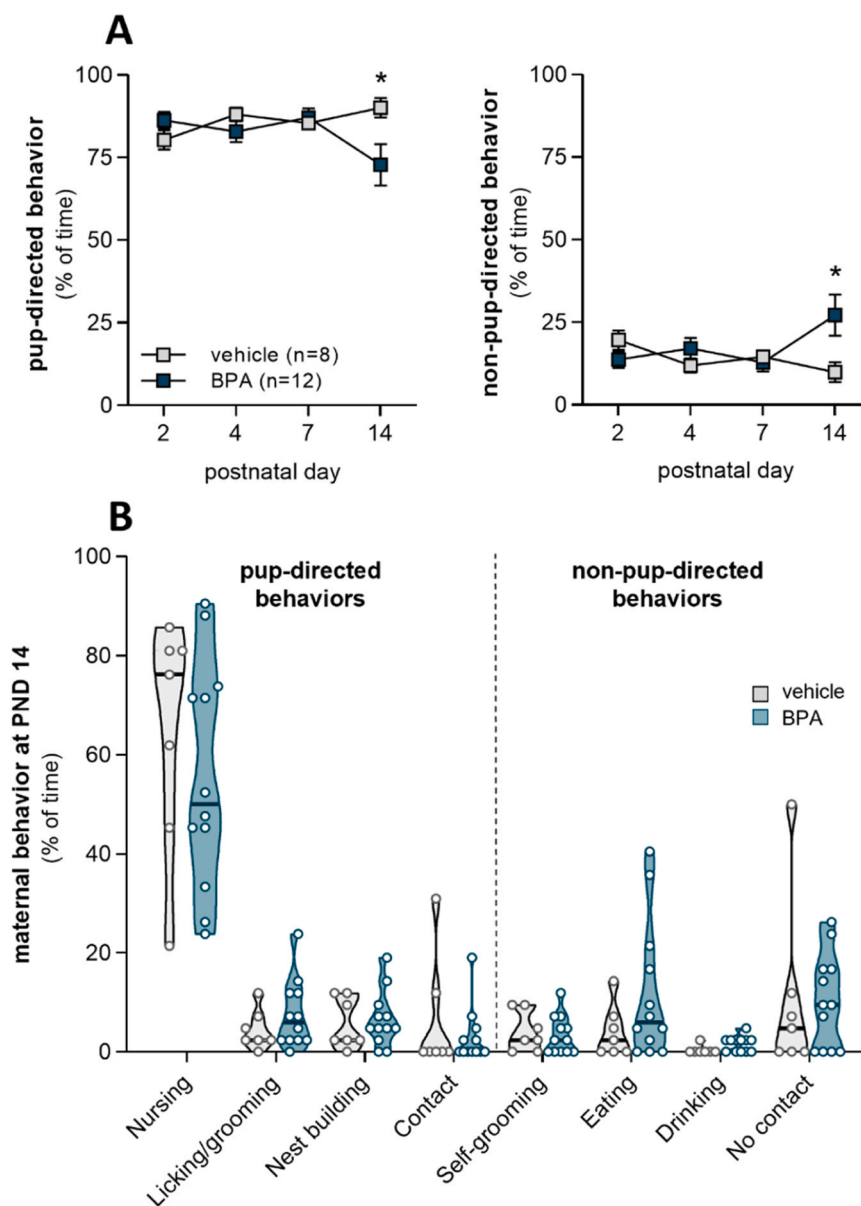


Fig. 2. Maternal behaviour of Djungarian hamsters exposed to vehicle (0.05 % ethanol) or BPA (5 μ g/kg/day) during gestation and lactation. (A) Percentage of the average time spent performing pup-directed behaviours (nursing, grooming, nest building, and contact with the pups) and non-pup-directed behaviours (self-grooming, eating, drinking, no contact with the pups) by vehicle- and BPA-exposed dams on postnatal days 2, 4, 7, and 14. Values are mean $\pm$ SEM ($n = 8$ –12/group). Grey squares represent data from vehicle-exposed hamsters, and blue squares represent data from BPA-exposed hamsters. (B) Percentage of time spent in different behaviours observed on postnatal day (PND) 14. Grey violins represent the distribution of data from vehicle-exposed hamsters and blue violins represent the distribution of data from BPA-exposed hamsters (with the black line indicating the median). *: $p < 0.05$. BPA, bisphenol A.

weight gain with a reduced food intake in BPA-exposed female hamsters, a subset of adult females was monitored in metabolic cages for a 64-hour period. Differences in metabolic parameters were observed during the nocturnal active period (Fig. 3E, Table 2), not during the diurnal inactive period. During the nocturnal phase, females exposed to BPA perinatally had reduced CO_2 production compared to control females, as well as a non-significant trend towards reduced ambulatory activity. The GLM analysis revealed interaction effects between body weight and BPA exposure for the nighttime parameters of energy expenditure, O_2 consumption, and CO_2 production (Table 2, Fig. 3F). These results suggest that, for the same body weight, females exposed to BPA expend less energy, consume less O_2 and produce less CO_2 at night.

In male hamsters, despite similar body weights at weaning (Fig. 3A), individuals exposed to BPA perinatally gained more weight ($+105\% \pm 12\%$) than those exposed to vehicle ($+67\% \pm 5\%$) from postnatal

week 4 (weaning) to 22 (Fig. 3B, C). Although BPA-exposed males gained more body weight, their cumulative food intake was similar to that of vehicle-exposed males (Fig. 3D), suggesting that the increased growth induced by BPA was not caused by increased food intake.

Concerning reproductive parameters, females exposed to either vehicle or BPA reached puberty between PND 50 and 52, with no significant impact of perinatal BPA exposure (Fig. 4A). In adulthood, circulating estradiol concentrations (Fig. 4B) and the relative weight of the ovaries and uteri were similar between the two groups of females (Fig. 4C). Morphometric analysis of ovaries showed a significant reduction in the number of atretic follicles, particularly in early atresia, in BPA-exposed females compared to vehicle-exposed females (Fig. 4D), while the number of corpora lutea was similar in both groups (Fig. 4E).

The onset of puberty in males occurred between PND 35 and 37 with no significant impact of perinatal exposure to BPA (Fig. 4F). In

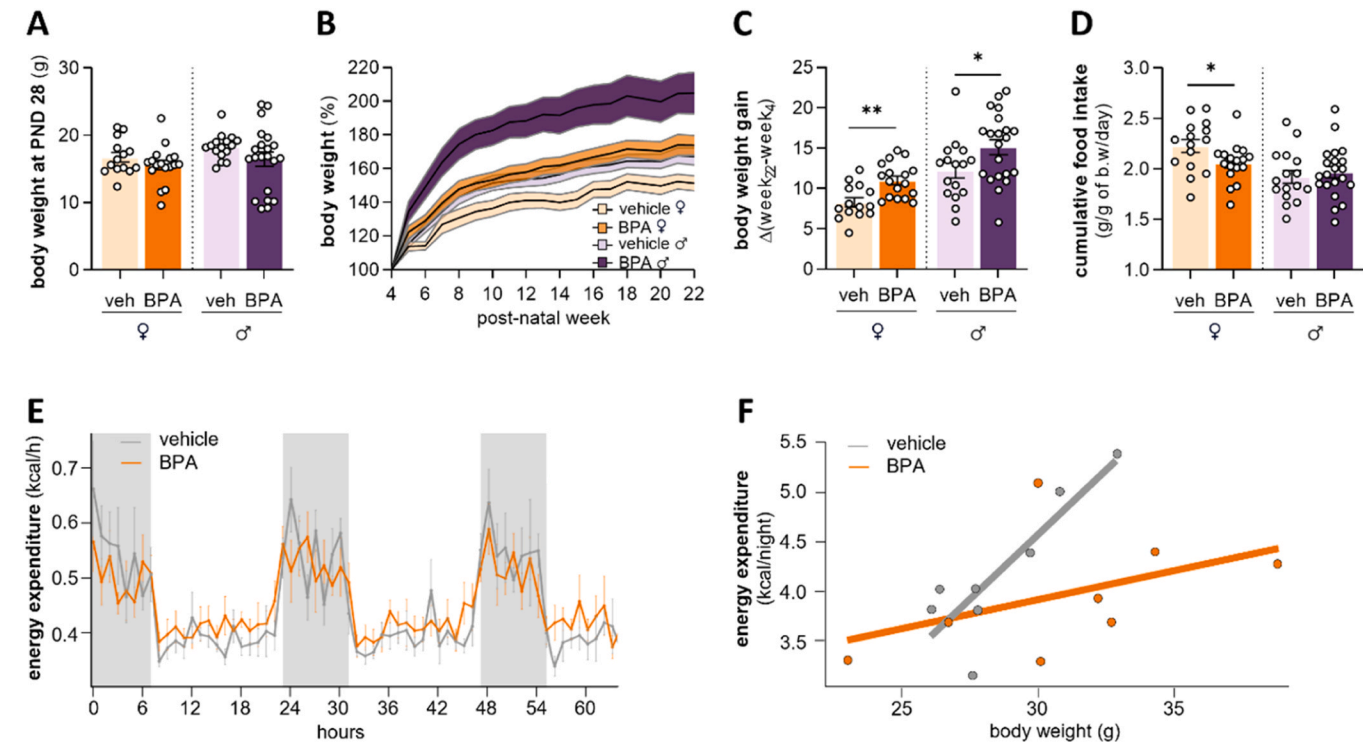


Fig. 3. Post-weaning and adult metabolic parameters of F1 female and male Djungarian hamsters perinatally exposed to vehicle or BPA. (A) Body weight of female and male pups at weaning. (B) Relative and (C) raw body weight gain of female and male hamsters from post-natal week 4 (weaning) to 22. (D) Cumulative food intake, from post-natal week 4–22, of female and male hamsters. (E) Energy expenditure of female hamsters averaged per hour over a 64-hour period (grey rectangles represent nocturnal phases). (F) A generalised linear model correlates individual averaged energy expenditure data (during the nocturnal period) with individual body weights to highlight the interaction effects between group and body weight. Individual values are presented with means $\pm$ SEM. For A, B, C, and D, $n = 14$ –17/group; for E and F, $n = 8$ /group (females only). *: $p < 0.05$, **: $p < 0.01$. Light orange bars, lines and dots represent data from vehicle-exposed female hamsters, and dark orange bars, lines and dots represent data from BPA-exposed female hamsters. Light purple bars, lines and dots represent data from vehicle-exposed male hamsters, and dark purple bars, lines and dots represent data from BPA-exposed male hamsters. BPA, bisphenol A; b.w., body weight; PND, post-natal day; veh: vehicle (0.05 % ethanol).

Table 2

Nocturnal metabolic parameters measured by indirect calorimetry, ambulatory activity and food intake of F1 female Djungarian hamsters perinatally exposed to vehicle or BPA. Values are mean $\pm$ SEM ($n = 8$ /group) of data recorded during the nighttime period of a 64-hour recording in metabolic cages. Metabolic parameters dependent on body weight (food intake, energy expenditure, O_2 consumption, CO_2 production) were analysed using a generalised linear model with body weight as a co-variate. *: $p < 0.05$, **: $p < 0.01$. The other parameters were analysed by one-way ANOVA. BPA, bisphenol A.

	Vehicle ($n = 8$)	BPA ($n = 8$)	Mass effect (p - value)	Group effect (p - value)	Interaction effect (p -value)
Food consumed (kcal/night)	4.6 ± 0.73	4.4 ± 0.58	0.0282 *	0.3066	ns
Energy expenditure (kcal/night)	4.2 ± 0.25	4.0 ± 0.22	0.0064 **	0.0532	0.0377 *
CO_2 consumption (ml/h)	115 ± 6.8	108 ± 5.9	0.0077 **	0.0589	0.0420 *
O_2 production (ml/h)	86 $\pm$ 5.5	82 $\pm$ 4.5	0.0032 **	0.0362 *	0.0252 *
Respiratory quotient	0.75 ± 0.012	0.76 ± 0.010	-	0.6418	-
Ambulatory activity (beam breaks/h)	287 ± 79	133 ± 22	-	0.0913	-

adulthood, both vehicle- and BPA-exposed males showed comparable

circulating testosterone concentrations (Fig. 4G) as well as relative testicular (Fig. 4H) and seminal vesicle (Fig. 4I) weights. Testicular morphometric analyses revealed no significant impact of perinatal BPA exposure on seminiferous tubule and lumen diameters, spermatogenic epithelium thickness (Fig. 4J), and seminiferous tubule area ratio (Fig. 4K).

3.3. Effects of perinatal BPA exposure on metabolic and reproductive adaptation to short photoperiod in F1 Djungarian hamsters

Along the 12-week SP, females that were perinatally exposed to BPA showed lower food intake, with a significant difference observed during the first 6 weeks (Fig. 5A, C). Consequently, they exhibited a higher percentage of body weight loss ($-18\% \pm 2\%$) than vehicle-exposed females ($-12\% \pm 2\%$), with a significant difference observed during the final 6 weeks of SP (Fig. 5A). Thus, 12 weeks after the transfer to SP, BPA-exposed females showed significantly greater body weight loss (Fig. 5D), and lower blood glucose levels (Fig. 5E) than vehicle-exposed females. The onset of winter coat, defined by a coat score > 2 , occurred at an average of 8 weeks SP for all females, with no significant impact of BPA exposure (data not shown), however, by the 12th week of SP, BPA-exposed females had significantly darker coats than vehicle-exposed females (Fig. 5F). The SP-induced reproductive quiescence, assessed by the vaginal orifice closure, occurred significantly earlier in BPA-exposed females than in vehicle-exposed females. Indeed, after 7 weeks of SP, vaginal closure was observed in 62.5 % of BPA-exposed female vs 12.5 % of vehicle-exposed females (Fig. 5G). In general, vaginal closure occurred 3 weeks earlier ($p = 0.07$) in BPA-exposed females compared with vehicle-exposed females (Fig. 5H). By the end of

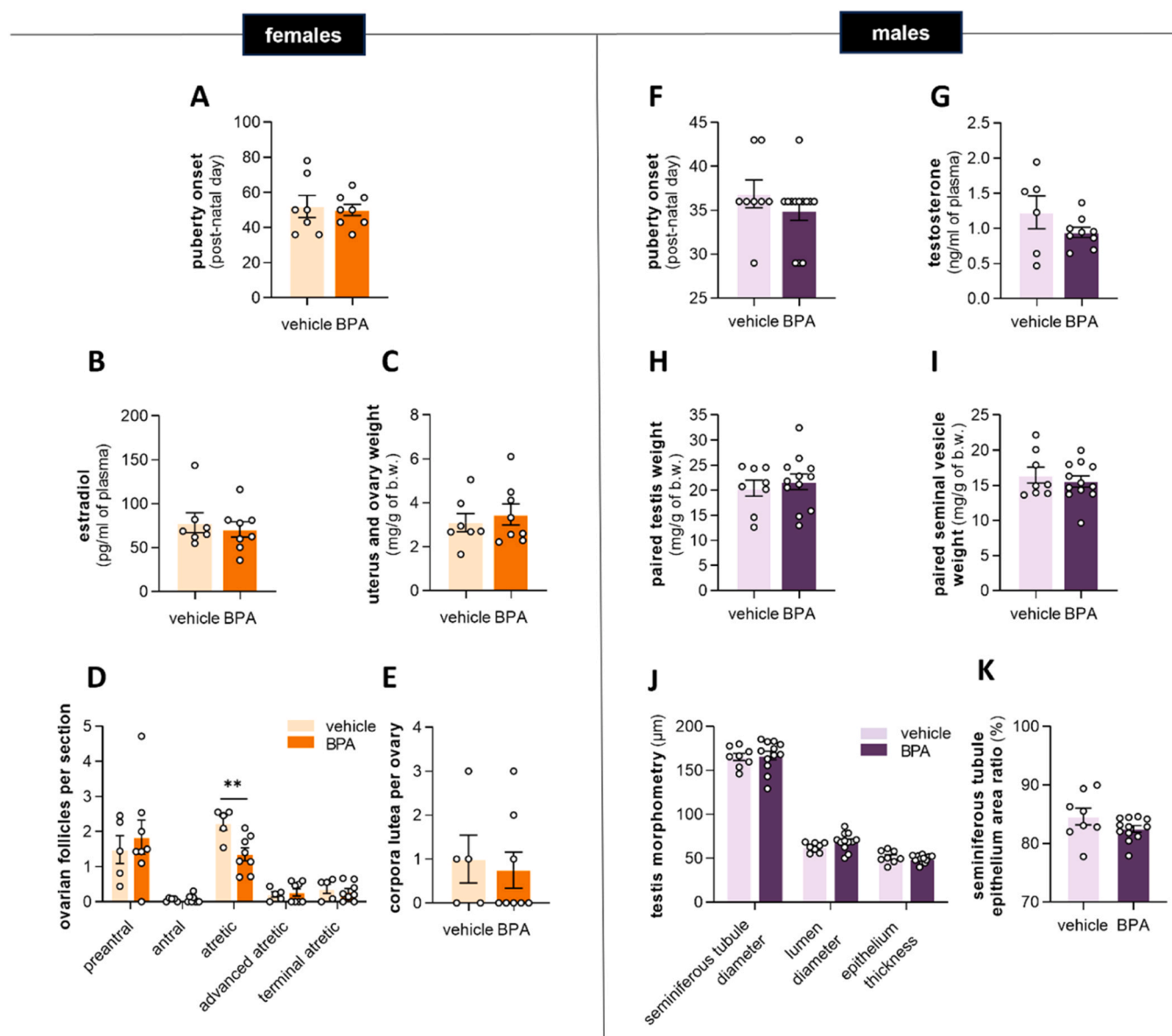


Fig. 4. Puberty onset and reproductive parameters at adulthood of F1 female and male Djungarian hamsters perinatally exposed to vehicle or BPA. For females, (A) age at vaginal opening. (B) Plasma concentrations of estradiol. (C) Relative weight of the uterus and ovaries. (D) Quantification of follicles and (E) corpora lutea. Values are presented with means $\pm$ SEM. $n = 5-8$ /group. **: $p < 0.01$. Light orange bars represent data from vehicle-exposed female hamsters, and dark orange bars represent data from BPA-exposed female hamsters. For males, (F) onset of puberty, defined by a threshold of an estimated testicular volume $> 100 \text{ mm}^3$ and the presence of complete balanopreputal separation. (G) Plasma concentrations of testosterone. Relative weights of the paired testis (H) and seminal vesicles (I) of adult hamsters. (J) Seminiferous tubule and lumen diameters, and seminiferous tubule epithelium thickness. (K) Seminiferous tubule epithelium area ratio (K). $n = 8-12$ /group. Light purple bars represent data from vehicle-exposed male hamsters, and dark purple bars represent data from BPA-exposed male hamsters. BPA, bisphenol A; b.w., body weight.

the 12-week SP adaptation period, all BPA- and vehicle- exposed female hamsters reached a fully quiescent reproductive phenotype, with similar low plasma estradiol concentrations (Fig. 5J) and low uterine and ovarian weights (Fig. 5L).

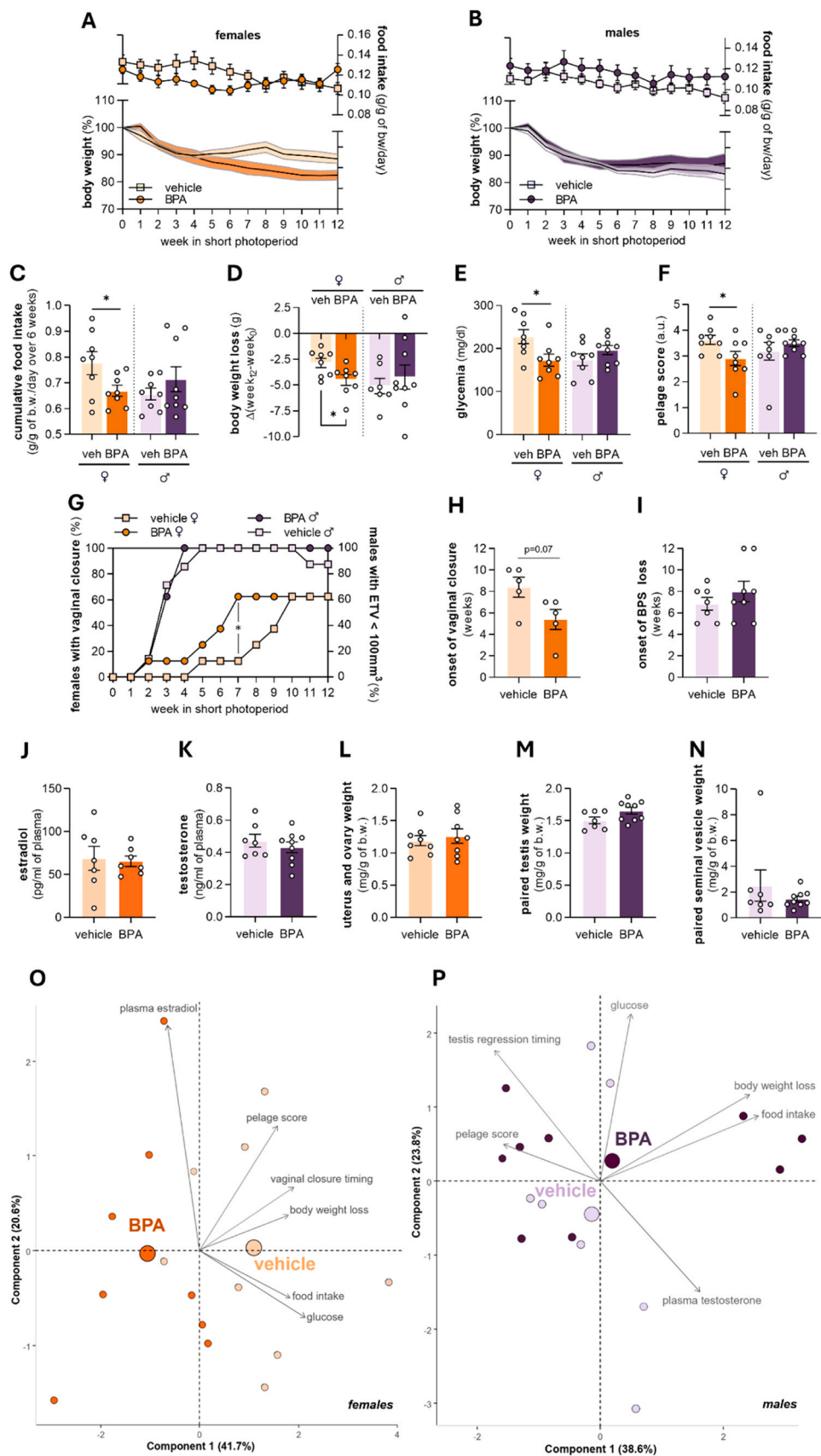
Unlike females, the metabolic and reproductive integration of male hamsters to SP was not affected by perinatal exposure to BPA. Males from both experimental groups exhibited a similar food intake (Fig. 5B, C), body weight loss (Fig. 5B, D), and final blood glucose levels (Fig. 5E). The onset (data not shown) and final bleaching of the winter coat (Fig. 5F) were similar in BPA- and vehicle-exposed male hamsters. SP-induced reproductive quiescence, characterised by a testicular volume $< 100 \text{ mm}^3$ by week 4 (Fig. 5G), BPS resorption by weeks 7–8 (Fig. 5I), low circulating testosterone (Fig. 5K), and complete regression of testes and seminal vesicles (Fig. 5M, N), remained unaffected by perinatal BPA

exposure in male hamsters.

Principal component analysis of multiple variables (body weight loss, food intake during the first 6 weeks of SP, onset of vaginal closure or testicular regression, pelage score, glucose, estradiol or testosterone plasma levels at the 12th week of SP), in both female (Fig. 5O) and male (Fig. 5P) hamsters transferred to SP, identified separate cluster groups for BPA- and vehicle-exposed female hamsters, but not for male hamsters. This indicates a significant sex-based difference in the effect of perinatal exposure on physiological adaptation to SP.

4. Discussion

Extensive studies have assessed the impact of EDCs such as BPA on reproduction and energy balance on traditional laboratory rodent



(caption on next page)

Fig. 5. Effect of perinatal exposure to BPA or vehicle on metabolic and reproductive phenotypes of F1 female and male Djungarian hamsters transferred from a long to a short photoperiod (SP) for 12 weeks. Percentage of body weight change and daily food intake during 12 weeks of SP in females (A) and males (B). (C) Cumulative food intake during the first 6 weeks of SP, (D) body weight loss during the 12 weeks of SP, (E) blood glucose levels at the 12th week of SP, and (F) final pelage score in females and males. (G) Percentage of females and males showing reproductive quiescence (vaginal orifice closure for females and estimated testicular volume (ETV) < 100 mm³ for males). (H) Time to onset of vaginal closure in females and (I) loss of balanopreputial separation in males. (J) Plasma concentrations of estradiol in females and (K) testosterone in males at week 12 of SP. Relative weight of (L) the uterus and ovaries in females, and (M) testis and (N) seminal vesicles in males. Individual values are presented with mean $\pm$ SEM, $n = 7\text{--}9/\text{group}$. *: $p < 0.05$. Principal component analysis biplots of metabolic and reproductive variables in female (O) and male (P) hamsters. The analysis includes body weight loss, food intake over the first 6 weeks of SP, onset of vaginal closure, pelage score, and glucose, estradiol, and testosterone plasma levels at week 12 of SP. Each point represents an individual animal ($n = 7\text{--}9/\text{group}$). Length of the arrows indicate the contribution of each variable to the principal components. Light orange bars, lines and dots represent data from vehicle-exposed female hamsters, and dark orange bars, lines and dots represent data from BPA-exposed female hamsters. Light purple bars, lines and dots represent data from vehicle-exposed male hamsters, and dark purple bars, lines and dots represent data from BPA-exposed male hamsters. BPA, bisphenol A; b.w., body weight.

models. BPA exposure has been reported to display adverse effects on both metabolic and reproductive systems through several mechanisms of action (Molina-López et al., 2023 for review). After entering the body through ingestion, inhalation, or direct contact, BPA interacts with hormonal receptors, including estrogen (Delfosse et al., 2012; Kitamura et al., 2005; Kuiper et al., 1998), androgen (Teng et al., 2013; Wang et al., 2017), and thyroid hormone (Moriyama et al., 2002; Sheng et al., 2012) receptors. It also modulates the availability of hormones to their receptors and induces epigenetic changes in endocrine organs or germ cells (reviewed by La Merrill et al., 2020). Although wildlife is exposed to BPA worldwide, the reproductive and metabolic health risks of such exposure are rarely assessed in animals adapting their physiology to environmental changes such as seasonal/photoperiodic variations. To the best of our knowledge, our study is the first to address the potential effects of BPA exposure, during gestation and lactation in a seasonal rodent model on: (1) fertility and maternal behaviour; (2) the onset of puberty, the growth of pups, and the function of the reproductive and energy systems in adulthood; and (3) the ability of the offspring to integrate the photoperiodic message and generate adapted physiological responses.

Here, in the Djungarian hamster, we report that maternal exposure to 5 μg of BPA/kg/day during gestation and lactation induced alterations in fertility and maternal care, characterised by an increase in the number of pregnancies and live pups, a reduction in postnatal mortality, and a reduction in pup-directed maternal behaviours at PND14, specifically showing a tendency for reduced nursing behaviours. After weaning, perinatally BPA-exposed male and female hamsters exhibited enhanced body weight growth. This was associated with a reduction in food intake and a decrease in energy expenditure for females, but no such changes for males. Perinatal BPA exposure did not affect the onset of puberty in male and female offspring, although an altered reproductive phenotype was observed in females marked by a decrease in ovarian atretic follicles. When transferred to an inhibitory SP to mimic a winter transition, adult females exposed to BPA perinatally presented accelerated physiological responses to SP, reflected in a higher reduction in food intake associated to larger body weight loss, reduced glycemia, and a faster reproductive quiescence and pelage whitening. Strikingly, in male hamsters, perinatal BPA exposure did not alter their reproductive and metabolic phenotype in adulthood nor following their physiological adaptation to SP transfer. These results highlight a marked sex dimorphism in the long-term effects of perinatal exposure to BPA in this seasonal rodent.

4.1. Perinatal exposure to BPA disrupts maternal behaviour in female hamsters and postnatal mortality

A tendency to a higher gestational success was observed in BPA-exposed Djungarian hamster dams in the two sets of breeding experiments. However, this repeated observation did not reach statistical significance ($p = 0.165$). In contrast, studies performed in laboratory rodents generally report that BPA exposure induces hypofertility (Cabaton et al., 2011; Ziv-Gal et al., 2015 for examples), a phenomenon that we did not observe here. In female rats and mice, BPA can cause

abnormalities in folliculogenesis and reproductive tract functions (López-Rodríguez et al., 2019; Santamaría et al., 2016; Zhang et al., 2012) and alter sexual behaviours (Farabollini et al., 2002; Reznikov et al., 2020; Picot et al., 2014). Here, in the Djungarian hamster, exposure to BPA probably did not affect mating behaviour, ovulation during the mating period, and embryo implantation, although complementary experiments would be required to confirm these assumptions. Moreover, the absence of a significant effect on fertility is consistent with findings from rats exposed to low doses of BPA, which also reported no change in fertility index (Ema et al., 2001). Exposure to environmental doses of BPA increases fertility in molluscs (Duft et al., 2003; Jobling et al., 2003), and enhances sexual behaviours in rats (Farabollini et al., 2002), indicating that BPA exposure does not necessarily induce hypofertility and that species-specific responses are likely. Early life BPA exposure did not affect Djungarian hamster's litter size but significantly reduced postnatal mortality, which contrasts with recent reports in mice showing that exposure to BPA, either directly to the dams or perinatally, can increase offspring postnatal mortality (Bonaldo et al., 2023; Shi et al., 2019). Altogether, these findings suggest that BPA has a peculiar species-dependent effect on pregnancy rates and postnatal mortality that requires further examination.

Djungarian hamster dams exposed to BPA showed an altered maternal behaviour towards their young on PND 14. This is consistent with the effects of BPA reported in other rodents, showing reduced licking and grooming of pups in rats (Della Seta et al., 2005) and mice (Johnson et al., 2015; Palanza et al., 2002), as well as an increase in out-of-nest and non-caring behaviours in mice (Palanza et al., 2002). However, this reduced maternal behaviour profile could not be associated with the higher survival rate observed in BPA-exposed pups, as mothers exhibited changes in maternal behaviour only at PND14, while still spending more than 70 % of their time with their pups. It could be possible that BPA-exposed pups differ in terms of early physiological robustness, thermoregulation, or suckling efficiency, although these mechanisms require further investigation.

Maternal behaviour is regulated by a complex neural network, which is modified during gestation and parturition under the influence of sensory stimulation and several hormones including estrogens, progesterone, oxytocin, and prolactin (Bridges, 2015; Keller et al., 2019). Disruption of the secretion and/or action of these hormones during this adaptive process is therefore likely to alter appropriate maternal behaviour (Keller et al., 2019 for review). Little is known about the mechanisms by which EDCs, and BPA in particular, alter maternal behavioural circuits. After exposure to BPA during gestation and lactation, alterations in estrogen receptor expression have been reported in the arcuate nucleus of dam rats (Aloisi et al., 2001) and in the oxytocin system in the paraventricular and supraoptic nuclei of dam mice (Bonaldo et al., 2023).

4.2. Exposure to BPA during gestation and lactation accelerates hamster offspring growth

At weaning, male and female hamster's body weight was not influenced by perinatal BPA exposure. However, later on, both male and

female hamsters perinatally exposed to BPA showed higher body weight gain than control hamsters. In mice, contradictory metabolic effects of perinatal exposure to BPA were reported with increased weight gain in both male and female pups (Nikaido et al., 2004; Rubin and Soto, 2009) or only in females (Miyawaki et al., 2007) or only in males (Le Corre et al., 2013). In Djungarian hamster, whether the body weight gain is correlated with an increase in fat or lean mass was not investigated, but some studies in mice and rats have reported that the BPA-induced weight gain is due to an increase in lean body mass (Le Corre et al., 2013; Miyawaki et al., 2007; Somme et al., 2009; Wei et al., 2011).

The BPA-induced increase in hamster's body weight was not associated to increased food intake, which was either reduced in females or similar in males. This suggests that female hamsters exposed to BPA during the perinatal period have a deficit in their energy expenditure. The indirect calorimetry study carried out on females confirmed this hypothesis, since the BPA-exposed females produced less CO₂ at night than the control females. Statistical analysis revealed that for a high body weight, energy expenditure at night was reduced in BPA-exposed females compared with control females, however with no effect on respiratory quotients. This is contrasting to a previous study in female mice reporting that perinatal exposure to BPA had no effect on nocturnal energy expenditure but increased their nocturnal respiratory quotients (Johnson et al., 2015). The authors suggested that perinatal exposure to BPA reduces the use of lipids to supply ATP, which promotes fat deposition. The reduction in energy expenditure observed in BPA-exposed female hamsters was associated with a trend towards reduced locomotor activity, an effect also found in mice exposed perinatally to BPA (Johnson et al., 2015). In 2013, Le Corre et al. observed that male mice exposed perinatally to BPA had reduced energy expenditure and a greater increase in body weight during growth, compared with controls, but their experimental conditions were different from those for hamsters, since the adult mice were fed a hyperlipidic diet. For technical reasons, it was not possible to study the energy expenditure of male Djungarian hamsters, but it would be interesting to check whether males exposed perinatally to BPA also show a deficit in energy expenditure.

4.3. Perinatal exposure to BPA does not affect puberty and the reproductive status of hamster offspring

Perinatal exposure to BPA did not alter the timing of puberty onset in male and female Djungarian hamster's offspring. In mice and rats, various effects of BPA were reported on the timing of puberty with results depending on the doses administered and the period of exposure. In females, perinatal BPA exposure has been reported to have no effect on puberty onset (Howdeshell et al., 1999; Losa-Ward et al., 2012; Murray et al., 2007; Tinwell et al., 2002) or to induce advanced (Honma et al., 2002; Nikaido et al., 2004; Odum et al., 2002) or delayed (Bonaldo et al., 2025; Franssen et al., 2016) puberty. Such effects have been linked to reproductive tract anomalies (Adewale et al., 2009), as well as central alterations, including altered pulsatile GnRH secretion (Fernández et al., 2009; Franssen et al., 2016) or decreased RFRP-3 fiber density and reduced contacts with GnRH neurons (Losa-Ward et al., 2012), and reduced kisspeptin mRNA expression (Navarro et al., 2009). In male rodents, only one study has reported delayed puberty in rats exposed perinatally to BPA (Oliveira et al., 2017), whereas the majority of studies found no effects (Bonaldo et al., 2025; Kato et al., 2006; Nagao et al., 1999; Tinwell et al., 2002).

Perinatal exposure to BPA did not affect reproductive organ weight or sex steroid concentration in adult female and male hamsters. However, histological analyses are important to assess potential BPA effect on gonadal functionality. Analysis of folliculogenesis in adult female hamsters revealed a significant decrease in the number of atretic follicles in those exposed to BPA compared to those exposed to the vehicle. A study in lambs also reported a decrease in follicular atresia following early postnatal BPA exposure (Rivera et al., 2015). One explanation for the observed decrease in atretic follicles is that BPA could have

accelerated the early depletion of the primordial follicle through excessive primordial activation (Hu et al., 2017), resulting in fewer follicles undergoing atresia in later adulthood. However, other studies in rats and mice reported an opposite effect of neonatal or adult exposure to BPA, which induced follicular atresia (López-Rodríguez et al., 2019; Tang et al., 2020).

4.4. Perinatal exposure to BPA disrupts female, not male, physiological adaptation to short photoperiod

Perinatal BPA exposure significantly altered the kinetics of metabolic and reproductive adaptations to SP in females, but not in males. This exposure accelerated the acquisition of SP reproductive and metabolic phenotypes in females, who reached reproductive quiescence earlier, eat less food, lost more body weight, and had a lower blood glucose level compared to control females. In contrast, the dynamics of reproductive and metabolic adaptation to SP were not affected by perinatal BPA exposure in males. Principal component analysis clearly illustrated the sex-dimorphic effect of perinatal BPA exposure on photoperiodic adaptation, distinguishing clusters between BPA- and vehicle-exposed females but not males.

Numerous studies have identified sex-dependent effects of BPA exposure on various outcomes, including obesity-related phenotypes (van Esterik et al., 2014), anxiety-like behaviour (Kundakovic et al., 2013), and spatial learning and exploratory behaviours (Jašarević et al., 2013). In a previous study in which adult Djungarian hamsters were exposed to BPA during photoperiodic transfers, we also observed strong sexual dimorphism in the effects of BPA, with females exhibiting delayed and males accelerated acquisition of the SP metabolic phenotype (Moralía et al., 2025). The long-lasting, sex dependent effect of BPA on photoperiodic integration in adulthood suggests that it involves organisational and/or epigenetic modes of action. Indeed, recent studies suggest that early-life exposure to BPA has long-term sexually dimorphic effects due to different epigenetic changes depending on sex (McCabe et al., 2017 for review).

As the photoperiod-induced reorganisation of the neuroendocrine circuits is well described (Dardente and Simonneaux, 2022 for review), further experiments should now investigate at which neuroendocrine level (pineal melatonin, hypothalamic T3, reproductive and metabolic hypothalamic peptides) perinatal BPA could be acting to alter SP-adaptation. Recent studies have demonstrated that the physiological adaptation of Djungarian hamster offspring to the upcoming season is differentially programmed by maternal short or long photoperiod (Sáenz de Miera et al., 2017; van Dalum et al., 2019). This photoperiod programming, mediated by the placental transmission of maternal melatonin, involves plastic and biochemical changes in hypothalamic tanycytes (Melum et al., 2024). Future studies should assess whether perinatal exposure to BPA disrupts the developmental trajectory of offspring by altering maternal melatoninergic signalling transmission and/or the downstream hypothalamic effectors.

5. Conclusion

This study on perinatal exposure, as well as our previous analysis on adult exposure (Moralía et al., 2025), provides evidence that the mechanisms underlying biological rhythms are affected by EDCs. This should be considered when assessing risk exposure for wildlife.

Oral exposure to BPA at an environmentally relevant dose during gestation and lactation impacts various outcomes in seasonal Djungarian hamsters, including maternal behaviour, postnatal mortality, pup growth, and the ability of adults to physiologically adapt to a winter-like photoperiod. It would now be interesting to assess the effects of perinatal BPA exposure on the physiological adaptation to an opposite photoperiodic transition (from a short to a long summer-like photoperiod) and even during consecutive sequences of photoperiodic transitions, to better mimic the seasonal cycles to which wild animals are

exposed. Furthermore, as has already been observed for adult exposure (Moralia et al., 2025) perinatal exposure of seasonal rodents to BPA has a stronger impact on female physiological responses to seasonal changes than on male.

This study emphasises that in seasonal rodents, as with other species including humans, the early stages of life are vulnerable to the impact of EDCs on the organisation of physiological functions. Future studies should assess whether these effects are mediated by direct action of maternal BPA on the offspring photoneuroendocrine pathway controlling seasonal adaptations, or indirectly due to altered maternal behaviour, which can induce developmental changes in the hypothalamus of pups (Champagne et al., 2006; Peña et al., 2013).

CRediT authorship contribution statement

Virginie Andry: Methodology. **Béatrice Bothorel:** Supervision, Investigation, Data curation. **Marie-Azélie Moralia:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Valérie Simonneaux:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was funded by the French agency for food, environmental and occupational health and safety (ANSES, PNR-EST 2018-069), the French Society for Endocrinology (SFE), and the Interdisciplinary Thematic Institute NeuroStra (ANR-10-IDEX-0002). We thank Dominique Ciocca, Sophie Reibel-Foisset, Nicolas Lethenet, and all the staff of the Chronobiotron's animal facility of Strasbourg for taking care of the hamsters. We thank Sakina Mhaouty-Kodja for her helpful discussions, and Yannick Goumon for the mass spectrometry supervision.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ecoenv.2026.119823](https://doi.org/10.1016/j.ecoenv.2026.119823).

Data availability

Data will be made available on request.

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