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Effects of IVF on mice offspring behavior and metabolism

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Motivation and Aim: *In-vitro* fertilization (IVF) has become a common assistive reproductive technology, however, it poses a number of risks, including increased incidence of obstetric complications and developmental disorders [1]. It is imperative to study the effects of IVF, not only to improve the outcomes of the procedure, but to gain more insight into the human embryogenesis in general. One of the less severe IVF effects on health, shown on large cohorts, is increased obesity, surprisingly without a significant increase in diabetes incidence [2]. In our laboratory we have observed similar effect in IVF-derived mice, that had higher body mass, but showed no signs of glucose intolerance. We hypothesized that increased body mass may be arise from differences in feeding behavior, locomotion or respiratory substrate utilization. In this study we assess whether differences between IVF-derived and naturally conceived CD1 mice are associated with behavioral differences.

Methods and Algorithms: Study included 2 groups of CD1 male mice: naturally conceived (control group, Ctrl, n=8) and IVF-derived (IVF group, n=10). IVF was conducted as previously described [3]. Mice were kept at artificial lighting conditions 10D:14L, lights-off event was considered a zeitgeber event (0:00 in zeitgeber time, ZT). At 10–11 weeks of age, mice were weighted, glucose tolerance test was conducted, and subsequently their behavior was recorded in the PhenoMaster cage PhenoMaster (TSE Systems, Germany). Recordings included locomotor activity, prolonged periods of inactivity (sleep), food and water consumption, indirect calorimetry (O_2 & CO_2 concentrations). PhenoMaster additionally calculates respiratory exchange ratio (CO_2 exhaled divided by O_2 consumed), an important metabolic parameter, that shows what substrate (fats or carbohydrates) the animal is oxidizing at the moment. We used Mann–Whitney U-test (two-sided) for all the group comparisons.

Results: IVF mice demonstrated significantly higher body mass than controls ($p < 0.01$) while areas under curve in glucose tolerance test were not significantly different. Surprisingly, average travelled distance of IVF mice was significantly higher than one of controls ($p < 0.05$), while food consumption per unit body mass was not significantly different. Average O_2 consumption and respiratory exchange ratio (RER) did not show any significant differences between groups. To better capture differences, we have averaged all behavioral time series across 4 days of experiment, to obtain a 24-hour long time series for each individual animal. We observed that the IVF group had a significant increase in RER at the end of the light phase (20–22 ZT, $p < 0.05$). Food consumption was also significantly higher around that period (hours 20, 23 ZT, $p < 0.05$). Travelled distance was significantly higher in IVF mice in many timepoints throughout the 24 hours. Daily sleep time was significantly lower in IVF group, compared to controls

both during light phase ($p < 0.001$), when mice typically have an a daily minimum of activity, and during dark phase ($p < 0.01$), when mice exhibit peak activity.
Conclusion: The data above demonstrates that IVF-derived mice tend to be more active and sleep less than naturally conceived ones. They also tend to have elevated respiratory exchange ratio during the light phase of the day, which is a sign of decreased lipid catabolism and increased glucose catabolism [4]. This suggests that IVF-derived mice higher body mass may be a result of differences in sleep-wake cycles.
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