Transplantation of abnormal white adipose tissue induced by obesogen tributyltin leads to abnormalities in the reproductive tract of female rats

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Introduction:

Tributyltin (TBT) is a well-known endocrine disrupting chemical associated with metabolic and reproductive dysfunctions. However, no studies have explored the effects of abnormal white adipose tissue (WAT) transplantation induced by TBT in the reproductive tract function in the female rats.

Objective:

To assess whether an abnormal WAT transplantation as result of TBT exposure impairs the reproductive parameters in the female rats.

Methods:

Female Wistar rats were treated daily with vehicle (ethanol 0.4%, CON rats, n = 5-8) or low dose of TBT (100 ng/kg/day, TBT rats, n = 5-8) for 15 days by gavage. The metabolic and estrous cycles were assessed during the exposure time. Further, serum samples were obtained to determined basal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen (E2), progesterone (P4), Anti-mullerian hormone (AMH) and testosterone (T) were by ELISA assays. WAT samples were collected to determined basal levels testosterone (T) by ELISA assays and to analyze gene expression of steroidogenic factors (*AR, star, cyp11a1, cyp17a1, cyp19a1, hsd17b1, and 5α-redutase*), an obesogenic marker (*ppary*) and histology. Other set of littermate rats was transplanted subcutaneously, with gonadal fat pads from CON and TBT rats (C-CON and C-TBT, respectively, n=5). We also performed SHAM controls (n=5). After 7 days following surgical procedure recovery, metabolic and reproductive parameters were assessed for 15 days. All the protocols were approved by the CEUA/UFES (Nº 16/2019).

Results:

CON and TBT rat donors showed similar metabolic parameters, such as body weight, adiposity and glucose metabolism ($p > 0.05$). Testosterone levels increased in the WAT of TBT rats compared to control rats ($p < 0.05$). TBT exposure induced a borderline increase in *17β-hsd* and *ppary* gene expression compared to control ($p = 0.05$ and $p = 0.05$). A borderline reduction in c*yp19a1* and *5α-redutase* gene expression was observed in TBT WAT tissue compared to CON ($p = 0.05$ and $p = 0.05$). Hypertrophy, oxidative stress and fibrosis in adipocytes were observed in TBT WAT tissue compared to control ($p < 0.05$). After WAT transplantation, C-TBT showed the reproductive tract abnormalities. Specifically, C-TBT rats presented irregular estrous cyclicity, spending more time in the proestrus and metestrus-diestrus phase, with longer cycle length compared with C-CON rats ($p < 0.05$). A Reduction in preantral and antral follicles and corpora lutea number were noted in C-TBT rats compared to C-CON rats ($p < 0.05$). Increased in cystice and atretice follicles were observed in C-TBT rats compared to C-CON rats ($p < 0.05$). A borderline

reduction of serum progesterone levels was found in C-TBT rats compared to C-CON rats ($p < 0.05$). Reduction in endometrium and myometrium area are observed in C-TBT rats compared to C-CON rats ($p < 0.05$). Reduction in uterine gland numbers were also noted in C-TBT rats compared to C-CON rats ($p< 0.05$). An increase in presence of mast cells in ovary and uterine of C-TBT rats were observed compared to C-CON rats ($p < 0.05$). An increase in collagen deposition in ovary and uterine of C-TBT rats were observed in C-CON rats ($p < 0.05$). No changes reproductive and metabolic were observed between sham and C-CON rats ($p > 0.05$).

Conclusion:

Collectively, these data suggest that an abnormal WAT transplantation as result of TBT exposure for short time impairs reproductive tract parameters in the female rats.

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