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Effects of betaine on histological and inflammatory changes of rat ovary caused by induction experimental polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most important endocrine disorders affecting about 5-10% of women in reproductive age. Betaine is a bioactive peptide that has an anti-inflammatory activity. The present study aimed to evaluate the effects of betaine on insulin resistance indices and inflammatory cytokines markers and histology alteration in rat ovary with experimental PCOS. This experimental study was performed on 48 female Wistar rats (170-200 g). PCOS was induced by administration of testosterone enanthate (1 mg/100g/day during 35 days). PCOS rats were treated with betaine (1% in drinking water) for 30 days. At the end of the experimental period, the insulin resistance markers (serum insulin and glucose concentrations the homeostasis model assessment of basal insulin resistance (HOMA-IR), serum estradiol (E2), progesterone (P4) and inflammatory cytokines were measured. The ovaries were also processed for histological study. PCOS induction resulted in insulin resistance, impaired E2, P4 production and elevation of tissue TNF-α, IL-1β levels. Moreover, a significant increase of ovarian cysts and atretic follicles and also a significant reduction in the early corpus luteum were observed in the ovarian tissue of the PCOS groups. Betaine treatment could reduce the inflammatory cytokines and improve steroid productions in PCOS rats. Betaine also restored normal Folliculogenesis by reducing atretic and cystic follicles. Our findings showed the beneficial effects of betaine in PCOS rats by improvement of folliculogenesis, suppression of inflammation in ovary.

Key words: Polycystic ovary syndrome, Ovary, Betaine, Folliculogenesis, Inflammation

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Refrences

Abbasi Samie, K., Tabandeh, MR., Afrough, M. (2020). Betaine ameliorates impaired steroidogenesis and apoptosis in mice granulosa cells induced by high glucose concentration. *Systems Biology in Reproductive Medicine*, 66(6): 400-409.

Abobaker, H., Hu, Y., Hou, Z., Sun, Q., Idriss, AA., Omer, NA. and Zhao, R. (2017). Dietary betaine supplementation increases adrenal expression of steroidogenic acute regulatory protein and yolk deposition of corticosterone in laying hens. Poultry Science, 96 (12), 4389-4398.

Amsterdam, A., Keren-Tal, I., Aharoni, D., Dantes, A., Land-Bracha, A., Rimon, E., Sasson, R. and Hirsh, L. (2003). Steroidogenesis and apoptosis in the mammalian ovary. *Steroids*, (68), 861-867.

Ballester, J., Munoz, MC., Domýnguez, J., Palomo, MJ., Rivera, M., Rigau, T., Guinovart, JJ. and Rodrýguez, GJE. (2007). Tungstate administration improves the sexual and reproductive function in female rats with streptozotocin-induced diabetes. *Human Reproduction*, 22(8), 2128-2135.

Beloosesky, R., Gold, R., Almog, B., Sasson, R., Dantes, A., land-Bracha, A. (2004). Induction of polycystic ovary by testosterone in immature female rate: Modulation of apoptosis and attenuation of glucose/insulin ratio. *Int J Mol Med*, 14(2)], 207-215.

Buettner, R., Parhofer, KG., Woenckhaus, M., Wrede, CE., Kunz-Schughart, LA., Schölmerich, J. and Bollheimer, LC. (2006). Defining high-fat-diet rat models: metabolic and molecular effects of different fat types. *Journal of Molecular Endocrinology*, 36 (3), 485-501.

Ciaraldi, TP., Aroda, V., Mudaliar, SR. (2013). Inflammatory cytokines and chemokines, skeletal muscle and polycystic ovary syndrome: Effects of pioglitazone and metformin treatment. *Metabolism*, 62(11), 1587-96.

Dhindsa, G., Bhatia, R., Dhindsa, M., Bhatia, V. (2004). Insulin resistance, insulin sensitization and inflammation in polycystic ovarian syndrome. *J Postgrad Med*, 50, 140-144.

Du, J., Shen, L., Tan, Z., Zhang, P., Zhao, X., Xu, Y., Yang, Q., Ma, J., Jiang, A.A., Tang, G. and Jiang, Y. (2018). Betaine supplementation enhances lipid metabolism and improves insulin resistance in mice fed a high-fat diet. *Nutrients*, 10(2), p.131.

Dunaif, A. (2012). Polycystic ovary syndrome in 2011: Genes, aging and sleep apnea in polycystic ovary syndrome. *Nature Reviews Endocrinology*, 8(2), 72.

Erickson, GF., and Shimasaki, S. (2003). The spatiotemporal expression pattern of the bone morphogenetic protein family in rat ovary cell types during the estrous cycle. *Reproductive Biology and Endocrinology*, 1(1), 9.

Gonza´lez, F. (2012). Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids*, 77, 300-305.

Grizales, AM., Patti, ME., Lin, AP., Beckman, JA., Sahni, VA., Cloutier, E. and Lee, A. (2018). Metabolic effects of betaine: a randomized clinical trial of betaine supplementation in prediabetes. *The Journal of Clinical Endocrinology & Metabolism*, 103 (8), 3038-3049.

Gual, P., Le Marchand-Brustel, Y. and Tanti, JF. (2005). Positive and negative regulation of insulin signaling through IRS-1 phosphorylation. *Biochimie*, 87 (1), 99-109.

Hossain, MA., Sharfaraz, A., Hasan, MDI., Somadder, PD., Haque, MDA., Md Rifat Sarker, Md., Monjurul, A., Wasaf Hasan, AM., Habibur Rahman, MD. (2022). Molecular docking and pharmacology study to explore bio-active compounds and underlying mechanisms of *Caesalpinia bonducella* on polycystic ovarian syndrome. *Informatics in Medicine Unlocked*. 33(10), 10-73.

Hu, ML., (1994). Measurement of protein thiol groups and glutathione in plasma. *Methods in enzymology*, 233, 380-385. https://doi.org/10.1016/S0076-6879(94)33044-1.

Ikeda, K., Baba, T., Morishita, M., Honnma, H., Endo, T., Kiya, T. (2014). Long-term treatment with dehydroepiandrosterone may lead to follicular atresia through interaction with anti-mullerian hormone. *J Ovarian Res.*, 7, 1-8

Joham, AE., Norman, RJ., Stener-Victorin, E., Legro, RS., Franks, S., Moran, LJ., Boyle, J., Teede, HJ., (2022). Polycystic ovary syndrome. *The Lancet Diabetes & Endocrinology*, 10, (9), 668-680.

Cook, C.L., Siow, Y., Brenner, A.G. & Fallat, M.E. (2002). Relationship between serum mullerian-inhibiting substance and other reproduction hormones in untreated women with polycystic ovary syndrome and Normal women. *Fertillity and Sterility, 77*(1), 141-146.

Kalhori, Z., Azadbakht, M., Bazdar, A., Zeinali, H. (2013). Polycystic ovary induction in Mouse by testosterone enanthate. *Journal of Fasa University of Medical Sciences*., 3(4), 387-91.

Kokabiyan, Z., Yaghmaei, P., Jameie, SB., Hajebrahimi, Z. (2022). Therapeutic Effects of Eugenol in Polycystic Ovarian Rats Induced by Estradiol Valerate: A Histopathological and A Biochemical Study. *International Journal of Fertility and Sterility*, 16, 3, 184-191.

Lo, J. C., Yang, J., Gunderson, E. P., Hararah,M. K., Gonzalez, J. R., & Ferrara, A. (2017). Risk of type 2 diabetes mellitus following gestational diabetes pregnancy inwomen with polycystic ovary syndrome. *Journal of Diabetes Research*, 5250162.

Mahamed RR, Maganhin CC, Sasso GRS, de Jesus Simões M, Baracat MCP, Baracat EC, et al., (2018). Metformin improves ovarian follicle dynamics by reducing theca cell proliferation and CYP-17 expression in an androgenized rat model. *Journal Ovarian Research*, 11, 18.

Marx, TL., Mehta, AE., (2003). Polycystic ovary syndrome: pathogenesis and treatment over the short and long term, *Clevel. Clin. J. Med*. 70 (1), 31–33.

Mendes Procopio, I., Aurelio Pereira-Sampaio, M., Silva Costa, W., Jose Barcellos Sampaio, F., Benchimol de Souza, D., (2021). Histomorphometric comparison of the cavernosum of rats submitted to euthanasis with ketamine and xylazine or isoflurane. *Acta Cirurgica Brasileira.* 36(11) e361103.

Misichronis, G., Georgopoulos, N., Marioli, D., Armeni, A., Katsikis, I., Piouka, A., Saltamavros, A., Roupas, N., Panidis, D. (2012). The influence of obesity on androstenedione to testosterone ratio in women with polycystic ovary syndrome (PCOS) and hyperandrogenemia. *Gynecol Endocrinol*, 28, 249–252.

Mu, YM., Yanase, T., Nishi, Y. (2000). Insulin sensitizer, troglitazone, directly inhibits aromatase activity in human ovarian granulosa cells. *Biochem. Biophys. Res. Com*. 271(3), 710 713.

Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF, (2013). Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): A systematic review and meta-analysis. *Human Reprort*; 19:268–88.

Nazari, M., Moghimipour, E., Tabandeh, MR. (2017). Betaine down regulates apelin gene expression in cardiac and adipose tissues of insulin resistant diabetic rats fed by high-calorie diet. *Int J Pept Res Ther*. 23(2),181–190.

Osibogun, O., Ogunmoroti, O., Michos, ED. (2020). Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovascular disease prevention. *Trends in Cardiovascular Medicine*, 30, (7), 399-404.

Popovic, M., Sartorius, G. and Christ-Crain, M., (2019). May. Chronic low-grade inflammation in polycystic ovary syndrome: is there a (patho)-physiological role for interleukin-1. In Seminars in immunopathology (pp. 1-13). Springer Berlin Heidelberg.

Shen, K., Shou, Y., Zhang, K. (2018). Effects on polycystic ovary syndrome of abdominal obesity treated with the dialing needling method at the abdomen. *BMJ* ,38(12),1273-6.

Shokri, F., Shokoohi, M., Roudi Rasht Abadi, A., & Kalarestaghi, H. (2019). The ameliorative effect of Galega officinalis extract on histological damages, oxidative stress induced by torsion-detorsion in adult rats' ovarian. *International Journal of Women's Health and Reproduction Sciences*, 7(1), 119–123.

Slow, S., Elmslie, J., Lever, M.Dietary. (2008). betaine and inflammation. *Am. Jor. Clin. Nutr.* 88, 247–8.

Spaczynski, RZ., Arici, A., Duleba, AJ. (1999). Tumor necrosis factor-α stimulates proliferation of rat ovarian theca-interstitial cells. *Biol Reprod*, 61, 993- 998.

Wang, Y., Zhu, W. (2012). Evaluation of Adiponectin, Resistin, IL-6, TNF-α in Obese and Non-Obese Women with Polycystic Ovary Syndrome. *Reprod Contracept*, 23(4), 237-44.

Wang, W., Zheng, J., Cui, N., Jiang, L., Zhou, H., Zhang, D., Hao, G. (2019). Baicalin ameliorates polycystic ovary syndrome through AMP-activated protein kinase. *Journal of Ovarian Research*, 12,109-121.

Wang, Z., Yao, T., Pini, M., Zhou, Z., Fantuzzi, G., Song, Z. (2010). Betaine improved adipose tissue function in mice fed a high-fat diet: a mechanism for hepatoprotective effect of betaine in nonalcoholic fatty liver disease. A*m J Physiol Gastrointest Liver Physiol*, 298(5), 634–642.

Xia, Y., Chen, S., Zhu, G., Huang, R., Yin, Y. and Ren, W. (2018). Betaine inhibits interleukin-1β production and release: potential mechanisms. *Frontiers in Immunology*, 9:12, 32-45.

Xiong, YL., Liang, XY., Yang, X., Li, Y., Wei, LN. (2011). Low-grade chronic inflammation in the peripheral blood and ovaries of women with polycystic ovarian syndrome. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 159, 148-150.

Yang, JL., Zhang, CP., Li, L., Huang, L., Ji, SY., Lu, CL., Fan, CH., Cai, H., Ren, Y., Hu, ZY., Gao, F., Liu, YX. (2010). Testosterone Induces Redistribution of Forkhead Box-3a and Down-Regulation of Growth and Differentiation Factor 9 Messenger Ribonucleic Acid Expression at Early Stage of Mouse Folliculogenesis. *Endocrinology*, 151(2),774–782.

Yu, J., Ding, C., Hua, ZH., Jiang, X., Wang, C. (2021). Protective effects of berberine in a rat model of polycystic ovary syndrome mediated via the PI3K/AKT pathway. J. *Obstet. Gynaecol. Res*. 47(5), 1789–1803.

Zafari Zangeneh F, Naghizadeh MM, Masoumi M. (2017). Polycystic ovary syndrome and circulating inflammatory markers. *Int J Reprod BioMed*, 15(6), 375-382.

Zhao, G., He, F., Wu, C., Li, P., Li, N., Deng, J. and Peng, Y. (2018). Betaine in inflammation: mechanistic aspects and applications. *Frontiers in Immunology*, 9:5, 134-153.