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Pesticides Induced Infertility: Targeting Ovarian Granulosa Cells

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Abstract

Female infertility is quite common these days, and among numerous causes, pesticides, directly or indirectly, forms an important reason for infertility among individuals. Studies suggest that pesticides modulate ovarian physiology but its' efficacies on granulosa cells inducing apoptosis determines the follicular fate. This in turn affects the oocyte production and quality. The role of granulosa cells as endocrine cells is significant and any alteration may produce temporary or permanent infertility. The study focuses upon the pesticide induced granulosa cells apoptosis and the probable mechanism associated with it. In addition, potentials of antioxidants in preventing granulosa cells apoptosis have been brought to light that may serve as boon in preventing pesticides induced infertility.

a) Conclusion: In conclusion, granulosa cells have huge significance in ovarian physiology that is potentially being affected by the toxicants like pesticides. The consequence of granulosa cells apoptosis may result in follicular atresia owing to permanent or temporary infertility. Thus, there is utmost need to add substantially to this area of research. Moreover, the potentials of antioxidants in combating the role of pesticides poisoning and preventing granulosa cells apoptosis need to be further explored from clinical aspects. The article will be beneficial in clinical cases to treat infertility in both targeted and non-targeted organisms.

Introduction

Pesticides form an important group of widely used agrochemicals whose ill effects have gone unnoticed for centuries in the light of its significances. Recent advances in the field of reproductive toxicology have explored the pesticide exposure risks owing to infertility [1]. In females, pesticides are found to be associated with estrous cycle irregularity, hormonal imbalance, follicular loss, ovulatory disruption, spontaneous abortions, still births etc. [2,3]. The resultant infertility is matter of great concern not only in humans but also other non-targeted organisms, especially domestic animals that are exposed directly or indirectly [4]. Though most of the pesticides are endocrine disruptors, targeting ovarian physiology but the least studied impact on granulosa cells have been found to be astonishing.

a) Granulosa cells - Predominant constituent of ovary: Indispensible role of oocyte in ovarian physiology and reproduction is quite well established. However, the incredible role played by GCs at different stages of follicular development in the oocyte production has been overlooked. Granulosa cells' growth and differentiation determines the follicular fate at each stage [5]. The oocytes are initially dependent on pre-granulosa cells during primordial follicular stage and later on, the differentiated and proliferating GCs that express various factors, controls and coordinates with the growth and maturating of oocyte [6]. They act as steroidogenic cells regulating folliculogenesis, ovulation and maintenance of pregnancy [7,8]. GCs differentiates into cumulous granulosa cells (cGCs) that maintains oocyte development and maturation, and mural granulosa cells (mGCs) that assists in growth of follicular antrum in paracrine fashion [9]. Thus, any alterations in structure and functions of granulosa cells largely affects oocyte production, both quality and quantity, that determines the fertility aspect of organisms.

b) Pesticidal toxicity-induces GCs' apoptosis: Among all other reproductive effects, pesticides affecting the survival of granulosa cells directly relates with infertility [10]. In support, Miller and co-workers have categorized follicular atresia on bases of granulosa cells apoptosis that relates >30% GCs apoptosis with late atretic follicle [11]. Several pesticides have been assessed for incidence of apoptosis within granulosa cells. Bisphenol A, endocrine disruptor used as plasticizer, was found to induce apoptosis and cause mitotic arrest within granulosa cells at micro molar concentrations in neonatal mouse ovaries by altering steroidogenesis and expression of associated genes [12]. It increased the expression of anti-apoptotic genes (Bad, Bcl2 and Bclxl) whereas increased the expression of catalase

genes with decreased glutathione peroxidase expression was also observed. Similar studies were done in porcine granulosa cells [13].

Organchloride pesticide, Methoxychlor and organophosphate pesticide, Malathion, both are found to be potent inducers of granulosa cell apoptosis as revealed via in vitro toxicological studies on rat and caprine granulosa cells [11,14-17]. Both the pesticides were found to alter the antioxidant enzymatic activity of the granulosa cells and targeted the genome producing DNA fragments and other nucleus associated anomalies like condensed chromatin, pyknosis, nuclear membrane blebbing, crescent shaped nucleus and fragmented nuclei [14,15]. Malathion increased the lipid stores within the GCs and damaged mitochondria [15]; while, Methoxychlor at low doses causes bax, an apoptotic gene, mediated apoptosis in granulosa cells [11] and increases the AMH production in the granulosa cells that inhibits folliculogenesis and transition from primordial to primary follicle [18]. Lindane, gamma-hexachlorocycloexane herbicide, affected the granulosa cell survival by inducing several Histomorphological alterations like decreased cytoplasmic processes between adjacent cells, chromatin condensation membrane blebbing etc [19]. Movento is insecticidal against sucking pests like aphis, thrips, silver leaf etc. by inhibiting lipid synthesis in them. Movento elevates the expression of FoxO1 expression and attenuates the VNN1 expression in granulose cells that is associated with GCs apoptosis, DNA damage, cell proliferation and differentiation [20]. FoxO transcription factors acts as regulators of oxidative stress and apoptosis by up-regulating associated genes' expressions. Studies have shown the expression of FOXO genes in rodent granulosa cells also [21].

c) Probable mechanisms of Pesticidal toxicity

Undoubtedly, any degenerative or regressive effects on granulosa cells will affect the growth of ovarian follicle and oocyte quality. Among several pesticides acting as reproductive toxicants, only few have been assessed for its toxicity on granulosa cells till date. These studies highlight granulosa cells' apoptosis as a consequence of Pesticidal toxicity. The histo-morphological changes found in GCs on exposure of pesticide reveal alterations in state and metabolic activity that serves as the main consequence of apoptosis. Loss of intercellular connections between granulosa cells hindered the intercellular communication necessary for GCs survival and oocyte development [22]. Most of the nuclear anomalies observed in GCs may have occurred down-line of caspases mediated cleavage lamins leading to nuclear fragmentation as observed [23].

Modifications in Lipid droplets storage and the mitochondrial morphology could account for the changes in steroidogenesis and energy production within the secretory granulosa cells signals the cells to undergo apoptosis [16]. Probably, most pesticides causes stress mediated activation of Caspases that initiates endonuclease activity of DNA fragmentation factor causing DNA fragmentation associated cell death [24]. Pesticides induce apoptosis within granulosa cells by modulating the expression of various pro-apoptotic and anti-apoptotic genes that leads to the suicidal activity of the cell [11,12]. Reactive oxygen species produced due to oxidative stress disrupt sugar moiety of DNA producing nicks that results in utilization of excess ATP for the DNA repair mechanism producing extra stress [25]. Though the causes can be numerous but the consequence of granulosa cell apoptosis will be one- follicular degeneration and infertility.

d) Anti-infertility Potentials of Antioxidants

Most of the signalling cascades associated with apoptosis induction utilize free radicles or ROS produced as messenger molecules; and antioxidants, capable of eliminating generated ROS can prove to be substantially beneficial in preventing pesticide induced granulosa cells apoptosis [26]. Few antioxidants have been reported to delay or inhibit apoptosis like α-tocopherol and N-acetylcysteine [27,28]. Other exogenous antioxidants like vitamins E, C, beta-carotene etc. protect against degenerative diseases associated with higher level of ROS generation [29]. Quercetin, a flavonoid dietary antioxidant, enhanced the intra-cellular antioxidant status thereby diminishing cadmium induced granulosa cells apoptosis by effective modulation of XIAP, Bax and Bcl-2 expression and lipid per oxidation [30]. Similarly, N-Acetyl-L-Cysteine, an excellent source of SH group has countered pesticides induced toxicity in numerous pesticide poisoning cases due to its radicles (hydroxyl, superoxide and peroxide) scavenging ability [31,32].

Studies have revealed the anti-apoptotic responses of NAC against Methoxychlor toxicity within granulosa cells thereby preventing apoptosis [17]. It has been found that NAC prevented granulosa cells apoptosis by up-regulating the activities of various antioxidant enzymes namely, superoxide dismutase, catalyse, glutathione-s-transferase, glutathione peroxidase etc. besides enhancing total antioxidant power and decreasing lipid per oxidation [17]. It is further hypothesized that NAC prevents MXC from activating NF-κB mediated suppression of catalyse and superoxide dismutase enzymes [33]. NAC supplementation has also been found to modulate the DNA fragmentation resulting in apoptosis within granulosa cells [17]. Studies also reveal Vitamin C and E as a potent anti-apoptotic-antioxidant preventing apoptosis and follicular atresia. Co-treatment of Vitamin E with cypermethrin up-regulated GLUT-1 synthesis that improved percentage atresia in preantral follicles probably by increasing glucose uptake by follicular cells that inhibits the expression of caspases-3, a pro-apoptotic molecules in follicular cells [34].

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