ENDOCRINE DISRUPTING CHEMICALS AND DOMESTIC ANIMALS

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Summary: Endocrine disrupting chemical is a term for a wide range of chemicals that could affect development and/or function of endocrine system in animals. First reports about potential endocrine disrupting effects of certain chemicals in the environment were published almost twenty years ago, based on the reports about problems with sexual development/differentiation of certain wild animals living in heavily contaminated environments like certain lakes in Florida, US. Subsequent studies have shown potential endocrine disrupting effects for many different chemical substances, ranging from pesticides, plastics, pharmaceuticals and others, and currently there is no known structure/function relationship that would suggest whether certain chemical might have endocrine disrupting properties. However, almost all studies showing endocrine disrupting properties have been performed in vitro or with laboratory animals so there is no conclusive answer whether such chemicals might pose a threat for human and animal health in everyday life. Interesting, though, are observations that male reproductive health has detoriated in the last decades. There are several reports that incidence of hypospadias, cryptorchidism and testicular cancer has increased, although these reports with the exception of testicular cancer, are often disputed. Similarly, several reports suggest fall in semen quality in human males in the last several decades, although again, this reports are often disputed and since there are no large prospective studies, we do not have a conclusive answer whether there really are any adverse effects occurring with human reproductive health. If such reports are reflecting real situation and if endocrine disrupting chemicals are involved in the etiology of such problems, one would expect similar trends to be observed also in domestic animals, which are usually exposed to similar environment as humans. However, there are very few studies systematically and chronologically examining reproductive health of domestic animals. Two published studies examined bull semen quality and could not detect detoriating quality. However, bulls in breeding centers are selected for their reproductive performance and therefore do not represent a situation in the normal population.

Key words: endocrine disruptors; reproduction; domestic animals

Introduction

It has been almost twenty years since term "endocrine disrupting chemical" was formed and first suggestions that certain chemicals in our environment could affect development and/or function of reproductive system appeared, although deleterious effects of chemicals like DDT and PCBs on wild populations of birds and some other animals was noted already in the sixties (1-3). First suggestions of direct effects of certain chemicals on development of sexu-

Received: 29 March 2010 Accepted for publication: 10 April 2010 al organs arose from observations about unusually high incidence of sexual development disorders in some wild animals in certain heavily polluted areas (1). At about the same time, first reports about increase in problems with male reproductive function appeared. Namely, several reports suggested that incidence of cryptorchidism and hypospadias increased during last 50 years (4-6) and there are several reports that semen quality in humans had detoriated during the same period (7). Although these findings are certainly not conclusive and are often disputed (8-13), there is one condition that is widely accepted as being on the rise and this is testicular cancer which is now the most common cancer in young males (14-18). Sharpe and Skkakebaek (19) suggested that all these problems could have a common origin in increased exposure to estrogens or chemicals with estrogen activity during male fetal development. This gave rise to an endocrine disruption hypothesis, proposing that different pollutants present in our environment could have deleterious effects on development and/or function of endocrine system. From initial observations that certain chemicals could affect development of male sexual organs, it is now thought that endocrine disrupting chemicals could influence other parts of endocrine system such as thyroid (20), and have perhaps even role in the obesity epidemics (21-23). Since many reports suggested that male reproductive health had detoriated in the last decades, it would be expected that similar trends would be also observed in domestic animals, since they are usually exposed to similar environment as humans. In the present article, evidence for effect of endocrine disrupting chemicals on domestic, in particularly farm, animals, will therefore be reviewed.

Endocrine disrupting chemicals

Initial suggestions that synthetic estrogens cold have deleterious role on development of sexual organs came from unfortunate episode with the use of strong synthetic estrogen Diethylstilboestrol (DES) in 60's and 70's as a treatment for risky pregnancies to prevent spontaneous abortions. Unfortunately, follow up studies have shown that DES had deleterious effect on the development of sexual organs in both male and female fetuses which was evident by increase in the vaginal clear cell carcinoma in female offspring and increased incidence of hypospadias and cryptorchidism in male offspring of treated women (24, 25). These reports were somewhat similar to the reports about increased incidence of hypospadias and cryptorchidism in general population, suggesting that common cause might connect both problems. This gave rise to the endocrine disrupting chemicals theory (19). Since first reports about endocrine disrupting chemicals, many man-made chemicals have been identified as being able to affect endocrine system in animals in vivo or in vitro. Endocrine disrupting chemicals are today considered as a varied group of chemicals that include certain pesticides (DDT, organophosphorous pesticides, possibly atrazine; 26-33), polychlorinated and polybromated biphenyls (PCBs and PBBs; 34-37), plasticizers (octylphenol, nonylphenol; 38-40), plastic components (phthalates, bisphenol A; 26, 41-43) and also some naturally occurring estrogenic compounds, so called phytoestrogens, such as coumestrol and genistin (26, 44). Although phytoestrogens have usually very low affinity for steroid hormone receptors, their high concentrations in many baby formulas and infant foods does present a cause for concern (44, 45).

Endocrine disrupting chemicals could affect different biochemical pathways. From initial observations that endocrine disrupting chemicals might act as estrogen agonists or androgen antagonists by binding to estrogen or androgen receptors, respectively, it became clear from in vitro studies that these chemicals could affect other receptors such as certain membrane receptors (for example serotonin and dopamine receptors), other nuclear receptors (thyroid receptors, peroxisome proliferator activated gamma receptors), and enzymatic pathways such as steroid hormone production (reviewed in 2). Endocrine disrupting chemicals are a diverse group of compounds with very diverse mode of action and at present, there is no known relationship between structure and function of such compounds that would allow predictions whether certain chemicals might have endocrine disrupting properties.

Many studies in laboratory animals have convincingly shown that endocrine disrupting compounds could affect endocrine development in laboratory animals. It is much less clear, however, if and how such chemicals affect human health. Although some reports from wild animals and humans from certain heavily polluted areas due to industrial spills convincingly demonstrated that some chemicals could indeed affect development and/or function of endocrine system in wild animals or humans, such cases are not really relevant for general human population, which is exposed to much lower doses of such chemicals (3, 28, 46). Therefore, at present we do not have an answer whether human reproductive health has really detoriated during the last several decades, and it is even less clear if endocrine disrupting compounds could have contributed to increased incidence of human reproductive problems and perhaps obesity.

Endocrine disrupting chemicals and animal health

If claims about detoriating reproductive health in humans are true and increase in reproductive problems in men is indeed caused at least partially by endocrine disrupting chemicals, one would expect similar trends to be observed also in domestic animals, which are usually exposed to similar environment as humans. Although there are no systematic records about reproductive health of pet/ companion animals, reproduction in farm animals is usually closely monitored for the purpose of successful breeding and good records exist for reproductive performance of such animals. Interestingly, though, only few studies addressed the issue of farm animal reproductive health from the endocrine disrupting chemicals perspective.

Endocrine disrupting chemicals and female reproductive health in farm animals

Reproductive success is one of the most important factors affecting economic success of dairy farms and reproduction of dairy cows is therefore closely monitored. Interestingly, there are several reports suggesting that reproductive success of dairy cows has indeed detoriated during recent decades (47-50), although it would be overwhelming simplification to connect this observation with endocrine disrupting chemicals. Reproduction in dairy cows is influenced by many different factors such as genetics, age, hormonal status, ovarian reserves as well as exogenous factors such as well being of animals including physical activity and sun light exposure. Therefore, it would be very challenging to connect any single factor with reproductive decline, especially considering that dairy production has intensified together with strong genetic selection of certain traits that might also affect successful reproduction. However, there are some field studies suggesting that certain pollutants could affect reproductive health of dairy cows (51) and endocrine disrupting chemicals do accumulate in liver and fat of animals grazing on pastures fertilized with sewage sludge (52). A number of laboratory studies, mostly in sheep, have shown that endocrine disrupting chemicals could indeed affect reproductive health of animals acting directly in the gonads or through the hypothalamic-pituitary system. Octylphenol has been shown to advance puberty in sheep and sows (40, 53). Furthermore, DES and some other endocrine disrupting chemicals could reduce FSH levels in sheep fetuses at midgestation, and this is thought to influence early follicular development in female lambs, causing premature puberty and some ovulatory problems in adult ewes (54, 55). Several endocrine disrupting chemicals have been also shown to affect steroid production in pig ovarian cells (56-58). These studies therefore suggest that female reproductive axis could be sensitive to some endocrine disrupting chemicals, although these were all laboratory studies and it is difficult to extrapolate such results directly to the general populations of farm animals.

Endocrine disrupting chemicals and male reproductive health in farm animals

Male mammals are thought to be especially vulnerable to the effects of endocrine disrupting chemicals due to the nature of development of their reproductive system. In male mammals, Sry gene present on the Y chromosome induces development of testis and testis with its hormonal secretions governs further development of male phenotype (59, 60). Since male fetal development is completely dependent on the proper secretion/exposure to sex steroid hormones, endocrine disrupting chemicals could interfere with these processes. Many studies in laboratory mice and rats have shown that different endocrine disrupting chemicals could indeed influence development of male sexual organs including testes, epididymes and prostates (reviewed in 2, 3). Studies in farm animals are scarce; nevertheless, there are some reports that endocrine disrupting chemicals could indeed affect development of male reproductive system also in sheep. Several studies have shown reduced sperm counts and increase in sperm abnormalities in rams exposed either pre- or postnatally to different estrogenic compounds such as DES; octylphenol and organochlorine pesticides (40, 54, 61) and one study reported that prepubertal exposure of pigs to estradiol or di-ethlyhexyil-phthalate affected testis size and testosterone secretion in adult boars. However, in this study animals were treated intramuscularly so it is difficult to extrapolate these results to usual, oral exposure to endocrine disrupting chemicals (62).

Bull breeding centers usually keep careful records of bulls' reproductive performance that would allow retrospective studies of bulls' semen characteristics. Surprisingly, though, there are only two such studies published, together with a meta-analysis study of published data (63-65). None of these three studies have reported any decline in any semen characteristic monitored during several decades, suggesting that no similar decline as reported in humans, has occurred in cattle. However, one has to keep in mind that such data is heavily confounded by the fact that bulls are selected also for their reproductive performance and therefore, such data could not be a true reflection of what might be happening in the normal population.

Conclusion

Although a number of studies in laboratory animals (and some in farm animals) have convincingly shown that endocrine disrupting chemicals could influence development and function of different cells in the testis and ovary such as Sertoli cells, Leydig cells, granulosa cells and oocytes and perhaps even adipocytes, there are no conclusive data that could link everyday exposure of humans or domestic animals to endocrine disrupting chemicals with their reproductive health. Therefore, carefully designed prospective studies will be needed to establish firstly, whether reproductive health in animals or humans has indeed detoriated in recent decades and, secondly, whether endocrine disrupting chemicals might have been involved in this problems.

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HORMONSKI MOTILCI PRI DOMAČIH ŽIVALIH

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Povzetek: Izraz hormonski ali endokrini motilci se uporablja za različne kemične snovi, ki lahko vplivajo na razvoj in/ali delovanje endokrinega sistema. Prva poročila o mogočem hormonskem delovanju posameznih kemičnih snovi v okolju so bila objavljena pred malo manj kot 20 leti kot poročila o povečanem pojavljanju nepravilno razvitih spolnih organov pri nekaterih divjih živalih, ki živijo v zelo onesnaženih območjih, kot je npr. okolica nekaterih jezer na Floridi v ZDA. Nadaljnje raziskave so pokazale, da lahko na delovanje endokrinega sistema vplivajo številne kemične snovi, kot so različni pesticidi, plastične, farmacevtske ter številne druge snovi. Zaenkrat ni znana povezava med strukturo kake molekule in njenim delovanjem, kar bi lahko nakazovalo, da bo določena kemična snov delovala kot hormonski motilec. Velika večina raziskav o hormonskih motilcih je bila narejena *in vitro* ali pri laboratorijskih živalih, tako da zaenkrat nimamo odgovora na vprašanje, ali hormonski motilci v nizkih koncentracijah lahko vplivajo na zdravje ljudi in živali tudi v naravnem okolju ob relativno nizki izpostavljenosti le-tem.

Približno istočasno kot prva poročila o morebitnem endokrinem delovanju nekaterih kemičnih snovi so se pojavila tudi prva poročila o naraščanju pojavljanja nepravilnosti na moških spolnih organih. Več raziskav je pokazalo, da se je povečalo število nepravilno razvitih sečnic (hiposadija) in nespuščenih mod in da narašča pogostnost raka na modih pri ljudeh v zadnjih desetletjih, vendar pa so ta poročila, razen tistih o naraščanju pogostnosti raka na modih, še vedno neenotna. V preteklih letih so se pojavila tudi poročila o zmanjševanju števila semenčic pri moških, vendar jih je izjemno težko potrditi ali ovreči, saj nimamo velikih načrtovanih raziskav, temveč smo odvisni le od retrospektivnih študij. Če podatki o povečevanju napak pri moških spolnih organih držijo in če so pri povečevanju težav udeleženi hormonski motilci iz okolja, bi pričakovali pojavljanje podobnih težav tudi pri domačih živalih, ki so običajno izpostavljene vplivu podobnega okolja kot ljudje. Vendar je izjemno malo raziskav, ki bi se ukvarjale z načrtnim in sistematičnim kronološkimo proučevanjem razmnoževanja pri domačih živalih. Dve retrospektivni raziskavi o kakovosti semena bikov iz osemenjevalnih centrov nista ugotovili zmanjševanja števila semenčic ali povečevanja napak na semenčicah, vendar pa je potrebno vedeti, da so biki v osemenjevalnih centrih selekcionirani tudi glede na njihove razmnoževalne sposobnosti, zaradi česar ta populacija ne odraža nujno dejanskega stanja v naravnem okolju.

Ključne besede: hormonski motilci; razmnoževanje; domače živali