Reproduction in Domestic Animals

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Review Article

Endocrine Disruptors in Domestic Animal Reproduction: A Clinical Issue?

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Contents
The objective of this review was to discuss whether endocrine disruption is a clinical concern in domestic animal reproduction. To that end, we firstly summarize the phenomenon of endocrine disruption, giving examples of the agents of concern and their effects on the mammalian reproductive system. Then there is a brief overview of the literature on endocrine disruptors and domestic animal reproduction. Finally, the clinical implications of endocrine disruptors on the reproductive system of farm animals as well as in dogs and cats are discussed. It is concluded that the evidence for clinical cases of endocrine disruption by chemical pollutants is weak, whereas for phytooestrogens, it is well established. However, there is concern that particular dogs and cats may be exposed to man-made endocrine disruptors.

Introduction

Endocrine disruption has emerged as a prominent policy and scientific issue since the report on chemically induced alterations in sexual development presented in 1992 by Clement and Colborn (Colborn and Clement 1992). For instance, the search term 'endocrine disrupt*' in the database 'Web of Science' had 324 hits in 1999 and increased to 6856 hits in 2014. Initially, an endocrine disruptor was regarded as a chemical compound able to bind to nuclear hormone receptors, in particular oestrogen receptors, and thereby act as an agonist or antagonist of the endocrine system. However, following more research in the field, it became evident that exogenous compounds could affect the endocrine system at several points along endocrine pathways, for example steroid biosynthesis and metabolism (Sanderson 2006; Tabb and Blumberg 2006; Diamanti-Kandarakis et al. 2009). The current international definition of an endocrine disruptors is thus: 'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) population' (Damstra et al. 2002). Yet, this definition is under reconsideration and might become more inclusive and be more based on endocrinological concepts than toxicological concepts, emphasizing the differences in effects effect at different life-stages (Zoeller et al. 2012).

Reports on the adverse effects on reproduction in different species have been presented in several reviews, for example effects on spermatogenesis (Veeramachaneni 2008; Yeung et al. 2011) and cryptorchidism (Virtanen and Adamsson 2012), altered time of onset of puberty (Magnusson and Ljungvall 2013), and disturbed sexual behaviour (Frye et al. 2012). Notably, endocrine disruptors mostly cause adverse and irreversible effects during development *in utero* and post-natally. In contrast, effects in the adult are mostly reversible when the exposure to the disruptor ceases (McLachlan et al. 2012).

The scientific and public concern that many environmental pollutants could be endocrine disruptors in humans as well as in wildlife has contributed to a rapid expansion of scientific literature in the field and there are several recent reviews on the subject (Hotchkiss et al. 2008; Diamanti-Kandarakis et al. 2009; Hamlin and Guillette 2010; Sharpe 2010; Fowler et al. 2012; Bergman et al. 2013). Examples of chemicals of concern are polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylenes (DDTs), polybrominated diphenylethers (PBDEs), perfluoroalkyl acids, bisphenol A (BPA) and phthalates (such as di(2-ethylhexyl) phthalate, DEHP). However, there are also non-anthropogenic phytooestrogens that may act as endocrine disruptors with clinical impact (Jefferson et al. 2012).

The objective of the current review was to give a brief overview of the literature on how livestock may contribute to the spreading of endocrine disruptors in the environment, on the extent that domestic animals, or cells from domestic animals, have been used to study metabolism and effects of endocrine disruptors and, finally, on the exposure of domestic animals to endocrine disruptors. With that background, we then focus on the known and potential clinical impact of anthropogenic and natural endocrine disruptors on domestic animal reproduction.

Research on endocrine disruptors and reproduction in domestic animals

Domestic animals relate to endocrine disruptors in many ways. One is the controversial use of synthetic steroid hormones as growth promoters in beef cattle in certain countries. It has been a shown that the soil and run-off from large feedlots contain large amounts of bioactive steroids that may affect wildlife and the environment around these cattle feeding operations (Bartelt-Hunt et al. 2012). However, even from live-

stock operations not using these kinds of growth promoters, there is leakage into the environment of endocrine active substances (endogenous) that may affect the wild fauna (Bartelt-Hunt et al. 2012; Cavallin et al. 2014). Also, pig manure may contain endocrine disrupting compounds in amounts that might be an environmental concern (Combalbert et al. 2012). A cautious conclusion from this literature is that manure from livestock operations – both those using as well as those not using endocrine growth promoters – may spread endocrine disruptors into the environment. Yet, more research is needed in this area before firm conclusions can be made.

There is also an increasing amount of literature from experimental studies in which domestic animals have been used to investigate endocrine disruption – for recent reviews, see Magnusson and Dencker (2010), Magnusson (2012) and Evans et al. (2014). These studies have been performed in both sexes and in various species such as goat (Oskam et al. 2005), sheep (Krogenaes et al. 2014; Corbel et al. 2015) and pig (Ljungvall et al. 2008; Gralén et al. 2012), looking at mechanisms of action as well as effects. It can be concluded from these studies that some effects are similar across species – including the well-studied laboratory species – whereas some are different. The latter might be due to differences in uptake of the endocrine disrupters from the intestines, differences in the metabolism of the endocrine disrupters, differences in the endocrine signalling and endocrine enzymes in the exposed species, etc. Extrapolation of these findings from such controlled experimental studies to a clinical situation must, however, be made with care. In the clinic or real life, the animal is often exposed to a mixture of compounds and the dose of the individual chemical is frequently lower than in the experimental situation.

The well-advanced reproductive biotechnology techniques for domestic animals have allowed the use of bovine and porcine *in vitro* maturation/fertilization models for studying endocrine disruptors, as recently reviewed by Santos et al. (2014) and previously by others (Brevini et al. 2005; Magnusson 2005). Cells or systems used are for instance oocytes (Grossman et al. 2012), co-culture of theca and granulosa cells (Gregoraszczuk et al. 2008a,b), Leydig cells (Castellanos et al. 2013), sperm (Mohamed et al. 2011; Lukac et al. 2013) and testicular interstitial cells (Pathirana et al. 2011). These studies provide important insights into the mechanism of action for several endocrine disruptors under strict controlled conditions on cells vital for reproductive success. These studies also indicate risks of effects from the examined compounds on the reproductive system in real life. However, often it is not possible to include the toxicokinetics and metabolic aspects of the compounds in these studies, which is why their clinical relevance is sometimes questioned.

Finally, there is a group of reports where concentrations of known endocrine disruptors seen in studies with laboratory rodents have been compared with those recorded in various tissues of domestic animals. In some cases, the health and performance of the animal itself has been the concern, as with dairy cows (Petro et al. 2010) and sheep (Rhind et al. 2011); sometimes the focus has been on food safety aspects such as in pork and beef (Glynn et al. 2009) or milk (Desiato et al. 2014); and occasionally, the animal has been used as a sentinel for chemical exposure such as in pet cats and dogs (Ali et al. 2013).

Endocrine disruption and reproduction in farm animals – clinical observations

Endocrine disruption is typically seen in species that are higher in the trophic ladder, as several of the anthropogenic compounds of concern are biomagnified in the food chain. In contrast, herbivorous domestic ruminants, being lower in the trophic ladder, are less likely to be exposed to high concentrations of anthropogenic endocrine disrupting substances. However, it has been suggested that animals grazing in areas near incineration plants might be exposed to high amounts of environmental pollutants with endocrine disrupting properties (Ingelido et al. 2009). In countries practicing the spreading of sewage sludge on pastures, concentrations of endocrine disrupting chemicals were analysed in cattle and sheep and regarded to be too low to impair reproductive performance (Petro et al. 2010; Rhind et al. 2010). Similarly, in a large survey in Sweden in the pig, which is often fed processed food and thereby at risk of eating chemical pollutants that have been biomagnified, the burden of organochlorine contaminants at slaughter was found to be close to the detection limit of the analytical methods used (Glynn et al. 2009).

One of the few reports in farm animals indicating endocrine disruption caused by environmental pollutants is regarding heifers that were drinking water in direct contact with a sewerage overflow. These animals showed increased age at first calving (Meijer et al. 1999). The reproduction of farmed animals that are higher up in the food chain, such as the American mink, could potentially be affected by diets high in fish from polluted waters. Indeed, organochlorines in polluted fish have been seen to cause decreased litter size and increased offspring mortality in mink (Aulerich and Ringer 1977; Bursian et al. 2013).

Although the evidence of endocrine disruption caused by environmental pollutants is weak, reports are more prominent when it comes to phytooestrogens. Perhaps the most classical is the so-called sweet clover disease, caused by formononetin and genistein that bind to the oestrogen receptors and modulate oestrogen enzymes resulting in prolapsed uterus and embryonic death in sheep (Cox 1978; Beck et al. 2005). Another well-known example is pigs suffering from various signs of hyperoestrogenism, such as vaginal prolapse, abortions and stillbirths, because of the phytooestrogen zearalenone (ZEA) produced by *Fusarium* fungi which contaminate cereals (reviewed by Fink-Gremmels and Malekinejad

2007; Zinedine et al. 2007). Despite the fact that ZEA has a non-steroidal structure, it does binds to both oestrogen receptor beta and alpha and thereby causes morphological and functional effects on the reproductive system. ZEA also interacts with endocrine enzyme systems. Species differences in hydroxylation systems are regarded as the cause of species differences in sensitivity to ZEA. It is well established that prepubertal gilts are very sensitive to ZEA, but there are also reports that prepubertal heifers may suffer from enlarged mammary glands and subsequent sterility. It is worth noting that following a change towards a warmer and more humid climate, the risk for more frequent contamination of cereals with ZEA may increase (Van Der Fels-Klerx et al. 2012).

Endocrine disruptors and dogs and cats

In comparison with the large number of studies regarding endocrine disruptors and the reproductive health of humans and wildlife, published studies on cats and dogs are very few. Pet animals share the home environment of the owners and may, therefore, be exposed to similar levels of endocrine disruptors. Because of this, dogs have been proposed as sentinels for human exposure to pollutants (Bukowski and Wartenberg 1997; Van der Schalie et al. 1999; Backer et al. 2001; Schmidt 2009). Similarly, cats have been suggested as sentinels for exposure to house dust (Mensching et al. 2012). In addition, dogs and cats may suffer from similar diseases as humans. For instance, mammary adenocarcinoma is comparable in dogs and humans, and associations with elevated concentrations of certain PCB congeners have been found in both species (Sévère et al. 2015).

In addition to the environmental exposure (indoor and outdoor) that dogs and cats share with their human companions, pet food is a route of exposure. For example, PBDEs have been found in both pet food and serum of dogs and cats (Dye et al. 2007; Venier and Hites 2011). Pet food has been found to contain phytooestrogens at levels that may have biological effects (Court and Freeman 2002; Cerundolo et al. 2004). Dog and cat food has also been found to contain BPA (Kang and Kondo 2002) as well as mycotoxins (Leung et al. 2006). Experimental studies showed that zearalenone (ZEA) affects the reproductive organs of bitches (Gajęcka 2013), but very few studies have examined adverse effects of BPA or other plasticizers (such as phthalates) in dogs. Dog toys have been found to contain both BPA and phthalates and, therefore, could represent another route of exposure (Wooten and Smith 2013; Nohrborg 2015).

Concluding remarks

Several solid experimental evidences, both *in vivo* and *in vitro*, demonstrate clinical effects and explain mechanisms of action of man-made endocrine disruptors on farm animal reproduction. In real life, under non-experimental conditions, there is, however, little, if any, evidence that man-made endocrine disruptors are a clinical concern for reproduction in domestic animals. In contrast, phytooestrogens are a well-known clinical issue that might become more prevalent following the climate change. Finally, it is also clear that cats and dogs are exposed to a variety of chemicals that may affect the reproductive system, which may call for words of caution.

Author Contributions

UM structured the study, reviewed the literature and wrote the manuscript. SP reviewed the literature and wrote the manuscript.

Conflict of Interest

None of the authors have any conflict of interest to declare.

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