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Review article

Progestins as endocrine disrupters in aquatic ecosystems: Concentrations, effects and risk assessment

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ABSTRACT

In aquatic ecosystems, progesterone (P4) and synthetic progestins (gestagens) originate from excretion by humans and livestock. Synthetic progestins are used for contraception and as P4 for medical treatments as well. Despite significant use, their ecotoxicological implications are poorly understood. Only about 50% of the progestins in use have been analyzed for their environmental occurrence and effects in aquatic organisms. Here we critically summarize concentrations and effects of progestins in aquatic systems. P4 and progestins were mostly detected when analyzed for, and they occurred in the low ng/L range in wastewater and surface water. In animal farm waste and runoff, they reached up to several μg/L. P4 and synthetic progestins act through progesterone receptors but they also interact with other steroid hormone receptors. They act on the hypothalamus–pituitary–gonad axis, lead to oocyte maturation in female and sperm motility in male fish. Additionally, other pathways are affected as well, including the circadian rhythm. Effects of P4, mifepristone and eleven synthetic progestins have been studied in fish and a few compounds in frogs and mussels. Environmental risks may be associated with P4, dydrogesterone and medroxyprogesterone acetate, where transcriptional effects were found at highest environmental levels. Reproductive effects occurred at higher levels. However, norethindrone, levonorgestrel and norgestrel compromised reproduction at environmental (ng/L) concentrations. Thus, some of the progestins are very active endocrine disrupters. This review summarizes the current state of the art and highlights risks for fish. Further research is needed into environmental concentrations and effects of non-investigated progestins, unexplored modes of action, and the activity of mixtures of progestins and other steroids to fully assess their environmental risks.

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1. Introduction

Pharmaceuticals are increasingly used by humans and in veterinary medicine. Some of them pose a risk to the environment (Fent et al., 2006). Among the most critical pharmaceuticals are steroid hormones. They interact at very low levels to evolutionary conserved receptors and exhibit similar effects as in humans (Christen et al., 2010). The consequences of such steroids are particularly important as they may act as endocrine disrupters. Endocrine disruption by natural and synthetic steroid hormones, as well as of chemicals, is of concern in aquatic ecosystems. Steroids are among the most potent endocrine disrupters (Länge et al., 2001; Pawlowski et al., 2004; Sumpter and Johnson, 2005; Jobling et al., 2006; Caldwell et al., 2008; Tyler and Jobling, 2008; Christen et al., 2010). They reach aquatic ecosystems from natural excretion by humans and livestock and from their use as contraceptives and from medical applications. Synthetic androgens and progestins are also used as growth promoters in livestock. Adverse effects have been demonstrated for 17α-ethinylestradiol (EE2) on fish reproduction (Länge et al., 2001; Pawlowski et al., 2004; Sumpter and Johnson, 2005; Runnalls et al., 2010; Hamilton et al., 2014), leading to population declines (Kidd et al., 2007), occurrence of intersex gonads (Jobling et al., 2006; Lange et al., 2011; Söffker and Tyler, 2012) and skewed sex ratio, all of which are of high ecological importance. Furthermore, the synthetic androgen trenbolone affected sex determination even at 9.2 ng/L (Morthorst et al., 2010) and decreased fecundity in fish (Ankley et al., 2003).

Steroids with progestogenic activity are called gestagens, progestogens or progestins. Often "environmental gestagens" is the term used for progestogenic compounds that are occurring in the environment, while "progestins" is used for synthetic progestogens/gestagenes. In this paper, the term "progestin" is used generally for progesterone receptor ligands eliciting progestogenic activity. Progestins came into focus in ecotoxicology only recently. In fish, synthetic progestins have an endocrine activity, similar to EE2 or trenbolone. They exhibited adverse effects on fertility and reproduction (Zeilinger et al., 2009; Paulos et al., 2010; Runnalls et al., 2013), altered hormone levels (Runnalls et al., 2013), induced transcriptional effects in adults (Zucchi et al., 2013, 2014) and embryos (Zucchi et al., 2012), altered sex development (Liang et al., 2015a,b) and induced development of male secondary sexual characteristics in female fish (Zeilinger et al., 2009; Runnalls et al., 2013). Together with synthetic estrogenic steroids, progestins are among the most important group of environmental pharmaceuticals of concern. However, in contrast to estrogens, progestins have received only little attention and their environmental risks are not sufficiently known. Therefore, there is an urgent need to further analyze the environmental consequences of these steroids in aquatic organisms.

The aim of this article is to critically review the state of the art in this field by focusing on the current literature on sources, environmental concentrations and effects of progesterone (P4) and synthetic progestins in aquatic organisms, with a focus on fish. Besides adding new and complementary information to previous reviews (Besse and Garric, 2009; Orlando and Ellestad, 2014; Kumar et al., 2015), this article provides a tentative risk assessment for fish based on current knowledge.

2. Progestin use and sources to the environment

Progesterone is involved in female menstrual cycle, pregnancy and embryogenesis of humans and vertebrates. As natural steroid hormone it is excreted by women but also by livestock in considerable amounts. There exists a series of about 20 synthetic steroids with progesterone-like activity (Sitruk-Ware and Nath, 2010). Synthetic progestins serve as key components in contraceptive pills and used in combination with synthetic estrogens such EE2. Their content in contraceptives is much higher than that of estrogens. In addition, P4 and progestins are prescribed in medicine (i.e. in hormone replacement therapy, endometriosis, cancer therapy, etc.). In many countries (i.e. USA, China) several synthetic progestins with androgenic activity find application also in livestock as growth promoters.

2.1. Classification

Synthetic progestins used for contraception are structurally related to either testosterone (estranes and gonanes) or progesterone (pregnanes and 19-norpregnanes) (Sitruk-Ware and Nath, 2010). In mammals, newer progestins bind more specifically to the progesterone receptor (PR) and minimize side-effects related to interactions with the androgen (AR), estrogen (ER) or glucocorticoid receptors (GR). For example, levonorgestrel (Besse and Garric, 2009; Svensson et al., 2013), norethisterone (Paulos et al., 2010), desogestrel and gestodene (Runnalls et al., 2013) have (anti)androgenic or (anti)estrogenic activities (Table 1). For long, "older" progestins with androgenic activity have been used (norethisterone, levonorgestrel, gestodene, medroxyprogesterone

Table 1
Progestagenic and other hormonal activities of synthetic progestins in mammals according to their structure. Drospirenone is a spirolactone derivative.
Adapted from Sitruk-Ware and Nath (2010) and Besse and Garric (2009).

Related to progesterone	Related to testosterone (19-nortestosterone derivatives)
Pure progestogenic	Partly estrogenic and androgenic
Compounds not yet used in contraceptives	Norethisterone
Antiandrogenic	Partly androgenic
Drospirenone	Levonorgestrel
Cyproterone acetate	Gestodene
Chlormadinone acetate	Desogestrel
Antialdosteronic	Antiandrogenic
Drospirenone	Dienogest
Partly glucocorticoid	Norgestimate
Medroxyprogesterone acetate	