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Discussion

On the unexpected reproductive impacts of metformin: A need for support and new directions for the evaluation of the impacts of pharmaceuticals in the environment

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1. General comments

The results presented in our paper (Niemuth and Klaper, 2015) regarding the reproductive impact of the anti-diabetic drug metformin highlight the need for encouraging the exploration of ways in which to improve of our methods for identifying the potential impact of pharmaceuticals in the environment. This research adds to evidence that the current process for characterizing environmental risk posed by pharmaceuticals and other emerging contaminants needs to be further evaluated. Exploratory studies, such as this one, provide an opportunity to improve our understanding of environmental risk and improve methods for assessing potential impacts to the environment. A letter by Sumpter et al. also supports the need for more studies on metformin, however, the authors also apply and repeat a list of assertions that they have published several times previously regarding research into the potential impacts of pharmaceuticals in the environment done by the ecotoxicology community including: the impacts found at relatively low exposure concentrations, results that do not follow predictions based on Kow, a purported violation of "the read–across hypothesis", and the publication of studies where the entire experiment has not been replicated possibly by another laboratory. In fact, Niemuth and Klaper (2015) is a part of a growing body of evidence that pharmaceuticals can act at relatively low concentrations on organisms in the environment, in this case metformin at concentrations found in wastewater effluent acts on the endocrine system and impacts steroidogenesis. The results call into question the idea that Kow is an appropriate tool for estimating risk. Metformin is a very hydrophilic compound and yet is still able to have impacts at an exposure concentration well below what would be predicted to result in a therapeutic plasma concentration based on Kow, most likely due to active transported into tissues which cannot be predicted based on Kow. In addition, our findings and those of others support rather than contradict the "read-across hypothesis," as metformin's impacts on the reproductive axis in humans were the basis of our hypothesis and support the idea of conservation of mechanisms across species. The potential negative consequences of this interaction are novel and point to the need to further elucidate the adverse outcome pathways involved. More cross-species comparisons, and data on the cross-talk among pathways is needed to further elucidate the mechanisms by which reproductive and other phenotypic changes may occur that are important to wildlife at low concentrations. Together all of these point to the need for more exploratory research and perhaps a broader reevaluation of how our current methods for predicting ecological impact may be improved.

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2. Need to further develop the "read-across hypothesis" in determining the risk of metformin and other pharmaceuticals

In theory, one might be able to predict the impacts of a pharmaceutical on organisms in the environment based on its interaction in humans. This idea of an ability to "read across" impacts seen in one organism to interpret what might happen in another is based on the idea that many pharmaceuticals target receptors and enzymes that are conserved across vertebrates and therefore data from mammalian studies can assist in determining the potential impact on organisms in the environment (e.g. Huggett et al., 2003; Winter et al., 2010).

Our study is one of a growing body of research that demonstrate the potential endocrine altering impacts of metformin in vertebrates. After finding a significant amount of metformin being emitted from the local wastewater treatment facilities in Milwaukee, and sustaining concentrations into Lake Michigan, we chose to conduct a toxicology assay at a concentration relevant to an exposure of fish sitting at the effluent of our local wastewater outfall, where several fish species congregate (Blair et al., 2013a,b). This is most likely an underestimate of exposure, as we found larger concentrations being emitted at times, and organisms experience these extremes, not average concentrations. In addition, exposure may be even greater in other locations, such as in wastewater-dominated streams, where exposure concentration can be identical to effluent (Luthy et al., 2015).

After a one month exposure of adult fathead minnows to metformin, we found a significant indication that metformin causes vitellogenin mRNA production in males (Niemuth et al., 2015), which has been shown by others to be an indicator of exposure to endocrine disrupting chemicals and an associated decline in reproduction (Bowman et al., 2000; Korte et al., 2000; Denslow et al., 2001; Kidd et al., 2007; Schmid et al., 2002). However, we did not find evidence of a change in the histology in the gonads or reproductive effects in our 28-day adult exposure study, and although plasma levels of vitellogenin were higher in metformin treated males this was not statistically different (Niemuth et al., 2015). We began to wonder about if this potential endocrine disruption may have a different impact in fish if they were exposed during development rather than adults. In the subsequent study (Niemuth and Klaper, 2015) we found that exposure from young to adult over a year caused a significant change in the size and most importantly reproduction in metformin treated fish. The most dramatic change was an obvious alteration of gonad histology in males, indicating the development of ova in the treated fish which were of such a significant percentage and severity (described in Fig. 2 in Niemuth and Klaper, 2015) that they were obvious and radically different from the controls.

Although this result may seem surprising and potentially unpredicted, we became interested in the reproductive consequences of metformin not only because of its relatively large presence in wastewater compared to other pharmaceuticals and the lack of significant ecotoxicology data, but because of the off-label prescription of metformin for the endocrine disorder polycystic ovarian syndrome (PCOS; Viollet et al., 2012). Its impacts on steroidogenesis in humans suggested that there might be a similar impact of this compound in other vertebrates such as fish. Others have suggested that side effects documented in humans may provide a mechanism by which to identify pharmaceuticals which may have an impact on important endpoints in ecological species (Ankley et al. 2007). In addition, off target uses of a medication can indicate alternative mechanisms of impact or cross-talk among pathways and should be investigated further in ecological studies and in assessing risk.

Others have shown that metformin exposure reduces LH and FSH secretion in response to GnRH stimulation in primary rat pituitary cells *in vitro* (Tosca et al., 2011); lowers Testosterone (T) in human and mouse testicular cells *in vitro* and reduces testicular T in offspring of mice administered metformin in pregnancy (Tartarin et al., 2012); reduces estradiol and progesterone levels as well as 3β-HSD, CYP11A1, and StAR protein levels in bovine granulosa cells *in vitro* (Tosca et al., 2007); induces expression of vitellogenin mRNA in the liver of adult male fathead minnows (FHM) in a 28-day exposure (Niemuth et al., 2015); and increases expression of *vtg*, *ERα*, *GnRH3*, and *CYP3A* mRNA in juvenile FHM in a dose-dependent manner (Crago et al., 2016). Niemuth and Klaper, 2015 is not an anomaly, but adds to the body of literature demonstrating metformin's endocrine impacts. The effects of metformin on portions of the endocrine system observed in our study as well as others and the off-target prescriptions for this drug for endocrine function in humans support a read-across of metformin influencing the endocrine system from humans to other vertebrates. The potential adverse outcome of a decrease in reproduction and intersex histology of males, however, was suprising.

We note that Sumpter et al. have pointed to the minor incidence of low severity spontaneous intersex in our controls (note that these were an average score of 0.2, not statistically different from 0 by a one-sample *t*-test) as suggestive of a potential confounding factor in our study. However, the spontaneous occurrence of intersex has been observed in FHM in labs elsewhere (Dietrich and Krieger, 2009; Yonkos et al., 2010), something that is common in many fish species (Bahamonde et al., 2013), including well-documented common incidence in model species such as medaka (Grim et al., 2007). The differences seen between those treated with metformin versus controls, in incidence and severity, documents the impact of the exposure.

Overall, the off-target use of metformin in humans related to fertility issues has provided an indication in this case that reproduction may be affected in other organisms and our data and that of others support this idea. More mechanistic data is clearly needed to better elucidate which pathways may be of interest for metformin at different time points and concentrations in fish as well as human models to evaluate the potential for "read-across" among organisms.

3. The need for better information as to which chemical characteristics are important: beyond Kow

It is obvious from not only this study but others (Scott et al., 2016; Ramirez et al., 2009; Nichols et al., 2015) that Log Kow is not a reliable predictor of environmental impacts of biologically active chemicals. The biology of the organism is critical and can determine uptake, subsequent binding by proteins, and interaction with receptors and tissues. Thus, adverse outcomes cannot be predicted by Kow alone.

As an example, metformin is effective as a drug for treating diabetes not because of its (lack of) hydrophobicity, but rather because it is actively transported into tissues by organic cation transporters (OCTs), leading to its active uptake and concentration in tissues. In fact, metformin's hydrophilicity also means that it must be actively excreted from tissues by MATEs, which is confirmed as co-treatment with cimetidine increases effective metformin dose by blocking excretion through Multidrug and Toxin Exclusion (MATE) channels (Ito et al., 2012; Graham et al., 2011). Thus, despite its hydrophilicity, metformin has been demonstrated to bioconcentrate to high magnitudes in plant tissues, as high as 20-fold, likely through active transport by OCTs (Eggen and Lillo, 2012). OCTs also likely exist in the gills of fish (Stott et al., 2015), so it's unsurprising that metformin was detected in whole-body tissue of

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