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Pharmaceuticals, illicit drugs and their metabolites in fish from Argentina: Implications for protected areas influenced by urbanization

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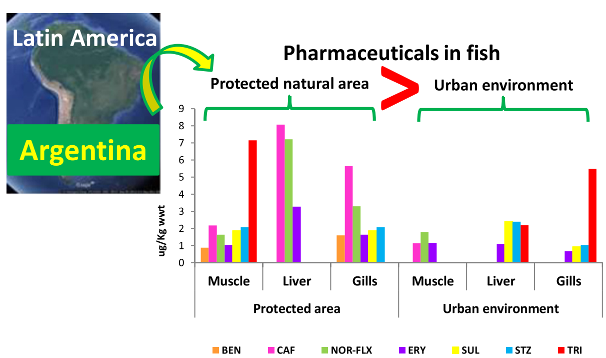
HIGHLIGHTS

- Fish from a protected area accumulated licit and illicit drugs and their metabolites.
- Caffeine and antibiotics were the major pharmaceuticals observed in fish.
- The macrolide erythromycin was ubiquitous in its first report in fish from Argentina.
- First identification of illicit drugs in fish from South America.
- Urban influences on aquatic contamination of protected areas require future attention.

GRAPHICAL ABSTRACT



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ABSTRACT

Because an understanding of aquatic bioaccumulation of human pharmaceuticals in Latin America is limited, this area was recently identified as a priority environmental quality research need. We examined bioaccumulation of twenty-seven pharmaceuticals, illicit drugs and their metabolites in muscle, liver and gills of multiple fish species (*Rhamdia quelen*, *Hypostomus commersoni*, *Hoplias lacerdae*, *Prochilodus lineatus*) from an urban river receiving wastewater discharges (Paraná) and a lotic system (Acaraguá) without direct wastewater sources, which runs through a protected area. All samples were analyzed using isotope-dilution liquid chromatography-tandem mass spectrometry. Caffeine, which was detected up to 13 μg/kg, and antibiotics were consistently detected in all fish. Among antibiotics, erythromycin was ubiquitous (0.7–5.6 μg/kg) but its tissue concentrations were lower than levels of sulfamethoxazole, sulfathiazole and trimethoprim (0.9–5.5 μg/kg), which are used in human medicine, aquaculture and livestock. Erythromycin bioaccumulation in fish is reported here from Argentina for the first time, though levels of antibiotics in edible muscles of these species were lower than the maximum residue limits for human consumption. We observed norfluoxetine, the primary active metabolite of the antidepressant fluoxetine, ranging from 1.1–9.1 μg/kg in fish. We further identified benzoylecgonine, a primary metabolite of cocaine, in fish from both study systems, representing the first observation an illicit drug or associated metabolites bioaccumulation in aquatic life from Argentina. Interestingly, high pharmaceutical levels were observed in fish from the Acaraguá river suggesting their transport into the protected area, from the

Abbreviations: ACE, Acetaminophen; AMTP, amitriptyline; AML, amlodipine; ARI, aripiprazole; BEN, benzoylecgonine; BUP, buprenorphine; CAF, caffeine; CBZ, carbamazepine; DES-Me-SER, desmethylsertraline; DCF, diclofenac; DLZ, diltiazem; DIP, diphenhydramine; DUL, duloxetine; ERY, erythromycin; FLX, fluoxetine; KET, ketamine; MPH, methylphenidate; NOR, norfloxacin; NOR-FLX, norfluoxetine; PROM, promethazine; PROP, propranolol; SER, sertraline; SUC, sucralose; SFD, sulfadimethoxine; SUL, sulfamethoxazole; STZ, sulfathiazole; TMP, trimethoprim.

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surrounding lands. Though fish from the Paraná river were sampled near WWTP discharges, pharmaceutical concentrations may have been reduced by hydrological and other environmental conditions, and biological differences among species. These findings, which observed bioaccumulation of select pharmaceuticals, their metabolites and illicit drugs in wild fish sampled inside a protected area, highlight the importance of developing an advanced understanding of urban influences on inland protected watersheds.

1. Introduction

Growing urbanization and frequent disposal of untreated sewage and treated effluent to water resources causes widespread contamination of freshwater and drinking supplies with contaminants of emerging concern (CECs) (Daughton, 2013). Among them, human and veterinary pharmaceuticals have raised an increasing concern due to their extensive use, physico-chemical characteristics, and continuous discharge to the aquatic environment (Evgenidou et al., 2015). Illicit drugs have been described as new and unexpected CECs with potent bioactive properties and unknown effects to organisms (Evgenidou et al., 2015). After consumption, pharmaceuticals and their metabolites are discharged into aquatic ecosystems via mainly wastewater effluents, landfill leaching, and manufacture, among others (Daughton, 2013). Since pharmaceuticals are highly water soluble, fish and other aquatic organisms accumulate these CECs primarily from water and also from food (Brooks et al., 2005; Du et al., 2014; Grabicova et al., 2015). Numerous studies worldwide have confirmed the occurrence of pharmaceuticals in a wide variety of environmental compartments showing that conventional wastewater treatment plants (WWTPs) are not effective to remove these CECs and current WWTP technologies vary among countries (Kookana et al., 2014).

Globally, ~80% of sewage production is released to the environment untreated (WWAP, 2017). These facts raise concern about the potential for bioaccumulation and associated adverse effects to aquatic wildlife (Daughton and Brooks, 2011), which was previously identified as a key research need to define risks of pharmaceuticals in the environment (Boxall et al., 2012; Rudd et al., 2014). Unfortunately, few studies have been focused on bioaccumulation of CECs in wastewater receiving water bodies or with biota under controlled laboratory conditions from Argentina (Cazenave et al., 2014; Dorelle et al., 2017; Elorriaga et al., 2013a, 2013b; Pérez et al., 2018; Valdés et al., 2014, 2015, 2016). In fact, Furley et al. (2018) recently identified better understanding relationships among pharmaceutical bioaccumulation, adverse effects and management as a priority research need for Latin America.

For this reason, the primary objective of the present study was to improve the knowledge about the occurrence of pharmaceuticals and illicit drugs, and their metabolites, in fish from the Atlantic Rain Forest rivers in the Misiones province, Argentina. We examined fish that were sampled in rivers commonly used for drinking and domestic purposes (>1,200,000 residents) but at the same time, receives untreated wastewater from diverse settlements. This research specifically examined bioaccumulation of twenty-seven selected pharmaceuticals, illicit drugs and their metabolites in three tissues of four fish species from the Paraná river, an urban system that receives wastewater discharge, and the Acaraguá river, which runs through a protected area without direct wastewater sources, in the Misiones province of Argentina. Potential influences of these human activities into the protected area were also considered.

2. Material and methods

2.1. Study area and sampling sites

Misiones province of Argentina has the largest remaining area of Atlantic Rain Forest (>10,000 km^2), which is one of the International Conservation Hotspots and one of the Global 200 World Wildlife Fund ecoregions (Izquierdo et al., 2008). However, this area has experienced rapid population growth and extensive deforestation during the last 40 years (Izquierdo et al., 2008). The region has nearly 1.7 million inhabitants (native and non-native population) with poor demographic and health conditions where sewers, wastewater service and improved drinking water supplies, are absent. Consequently, communities commonly use rivers for both disposing wastewater and direct consumption and domestic use. Moreover, various anthropogenic activities, such as towns, agriculture, deforestation, livestock, aquaculture and industries depend on and release contaminants to the water resources in this area (Avigliano and Schenone, 2015).

As introduced above, fish were collected inside at the protected area called "Antonia Ramos Research Center" (CIAR) in the Acaraguá river (27°26′S 54°56′W), and in the Paraná river (27°22′S 55°53′W) close to Posadas city, an area with over 360,000 inhabitants (Fig. 1). No WWTP effluents discharges are found in the protected area, which includes >750 ha of native rain forest, promoting the biodiversity conservation. The Acaraguá river is a higher gradient mountain river running through the protected area; however, upstream of our sampling site, this river receives runoff from agriculture and sewage from small towns, with extremely vulnerable socioeconomic conditions. In contrast, the Paraná river is influenced by several human activities, such as industries, agriculture, livestock and urbanization. In the present study, fish were sampled close to the discharge of two WWTPs, with secondary treatment, in Posadas (Fig. 1). This sampling site was specifically located upstream from the Yacyretá impoundment.

2.2. Fish collection

Fish species were selected because they are representative of neotropical communities with ecological relevance and economic importance to the local residents. *Rhamdia quelen* (Heptapteridae) is a bottom dwelling catfish that feeds on detritus, invertebrates and small fish. *Hypostomus commersoni* (Loricariidae) is an armored bottom-dwelling detritivorous/periphytivorous catfish. *Hoplias lacerdae* (Erythrinidae) or tararira, is a higher trophic level piscivorous predators. *Prochilodus lineatus* (Prochilodontidae) or streaked prochilod is a strict detritivor, previously identified as a useful bioindicator of aquatic pollution (Colombo et al., 2011; Pérez et al., 2018; Santos-Silva et al., 2018).

Sampling of the two study systems occurred at midday and samples from each river were collected on consecutive days in May 2016. General water conditions, including pH, water temperature, turbidity (NTU), dissolved oxygen (mg/L), water conductivity (μS/cm) and total suspended solids (TSS, mg/L), were measured at each sampling site at midday using a calibrated multiparametric probe Horiba U-52 (Kyoto, Japan). All fish were then collected following standard fishing procedures with multi filament gillnet and transported frozen to the laboratory. Muscle, liver and gills tissues were dissected, wrapped in pre-cleaned aluminum foil and stored at −20 °C until analyses. A total of thirty ($n = 30$) samples from the four study species were analyzed. Detailed information regarding biological characteristics of these fish is provided in the electronic supplementary material (Table S1).