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The biological effects of antidepressants on the molluscs and crustaceans: A review

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ABSTRACT

Antidepressants are among the most commonly detected human pharmaceuticals in the aquatic environment. Since their mode of action is by modulating the neurotransmitters serotonin, dopamine, and norepinephrine, aquatic invertebrates who possess transporters and receptors sensitive to activation by these pharmaceuticals are potentially affected by them. We review the various types of antidepressants, their occurrence and concentrations in aquatic environments, and the actions of neurohormones modulated by antidepressants in molluscs and crustaceans. Recent studies on the effects of antidepressants on these two important groups show that molluscan reproductive and locomotory systems are affected by antidepressants at environmentally relevant concentrations. In particular, antidepressants affect spawning and larval release in bivalves and disrupt locomotion and reduce fecundity in snails. In crustaceans, antidepressants affect freshwater amphipod activity patterns, marine amphipod photo- and geotactic behavior, crayfish aggression, and daphnid reproduction and development. We note with interest the occurrence of non-monotonic dose responses curves in many studies on effects of antidepressants on aquatic animals, often with effects at low concentrations, but not at higher concentrations, and we suggest future experiments consider testing a broader range of concentrations. Furthermore, we consider invertebrate immune responses, genomic and transcriptomic sequencing of invertebrate genes, and the ever-present and overwhelming question of how contaminant mixtures could affect the action of neurohormones as topics for future study. In addressing the question, if antidepressants affect aquatic invertebrates at concentrations currently found in the environment, there is strong evidence to suggest the answer is yes. Furthermore, the examples highlighted in this review provide compelling evidence that the effects could be quite multifaceted across a variety of biological systems.

1. Antidepressants in the aquatic environment

1.1. Background

The release of human pharmaceuticals and personal care products into aquatic ecosystems continues to be a serious environmental problem. There is a staggering list of prescription drugs passed from humans to wastewater treatment plants and into receiving streams, estuaries, or oceans by direct consumption, metabolism, and excretion or by toilet flushing of old prescriptions, that have been detected in water, sediment, and organisms. Environmental scientists and aquatic toxicologists have been aware of the problem since the 1970–1980s (Hignite and Azarnoff, 1977; Richardson and Bowron, 1985), but starting in the late 1990s concern became more intensified. In 1999, a seminal paper by Daughton and Ternes brought pharmaceutical and personal care product pollution to the forefront of aquatic research and set into motion studies in the current fields of fate, effects, and assessments of such pharmaceutical pollution (Daughton and Ternes, 1999). Thus, there has been a growing number of studies addressing effects of human pharmaceuticals on aquatic animals. There are excellent reviews by Kummerer (2008); Daughton and Brooks (2011); Boxall et al. (2012); Brausch et al. (2012); Brooks and Huggett (2012).

While there are literally hundreds of human pharmaceuticals excreted and which end up in the aquatic environment, those that are destined to have an effect on the physiology of aquatic invertebrates are ones that would interact with evolutionarily well conserved transporter and receptor proteins. Furthermore, there are model organisms whose physiological systems and their regulation by such proteins are well understood. Since molluscs such as the sea hare *Aplysia* and crustaceans like crayfish have been model organisms in neurophysiological research for decades, these systems and the drugs that modulate them are well understood. Human antidepressants are widely prescribed drugs throughout

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the developed world and their mode of action is by modulating neurotransmission in the human brain. But in addition, early laboratory studies (Kulkarni et al., 1992; Sarojini et al., 1993) showed that some antidepressants have an effect on critical invertebrate physiological functions such as ovarian and testicular growth.

In this paper we review the modulatory effects of antidepressants on various physiological systems in molluscs and crustaceans, two groups of non-target aquatic invertebrates that are numerically dominant and speciose, and thus ecologically important. We review the data on environmental concentrations of antidepressants, link this information with the known action of neurohormones, discuss recent studies showing effects of antidepressants on molluscs and crustaceans, and suggest important questions for future research.

1.2. Types of antidepressants

There are several different types of antidepressants from tricyclics like imipramine and clomipramine which block serotonin and norepinephrine reuptake transporters to monoamine oxidase inhibitors which blocks the enzyme that digests neurotransmitters such as serotonin and dopamine. By far the most widely prescribed antidepressants worldwide are selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine) and Zoloft (sertraline) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) such as Effexor (venlafaxine) and Cymbalta (duloxetine). The mode of action of SSRIs and SSNRIs is similar to that of tricyclics in that they bind to and inhibit pre-synaptic reuptake transport proteins. These proteins normally recycle neurotransmitters back into the pre-synaptic terminal. Inhibition of these transporters allows neurotransmitters to remain in the synaptic cleft longer. Thus, all of the aforementioned antidepressants work by modulation of serotonergic, dopaminergic, or noradrenergic neurotransmission. Because SSRIs and SSNRIs are the most widely prescribed antidepressants, they are the most commonly detected in samples of wastewater influent, effluent, raw sewage, and downstream from treatment plants. The vast majority of published studies on the effects of antidepressants on molluscs and crustaceans have utilized these antidepressants.

1.3. Concentrations in the aquatic environment

Within the last decade, a large number of studies have measured active pharmaceutical ingredients (APIs) in various aquatic systems worldwide. Studies of measured pharmaceutical concentrations include those from freshwater (Kolpin et al., 2002), from estuaries (Thomas and Hilton, 2004; Roberts and Thomas, 2006; Benotti and Brownawell, 2007; Madureira et al., 2010), in the open ocean (Choong et al., 2006; Pait et al., 2006), in drinking water (Zwiener, 2007), and biosolids (Jones-Lepp and Stevens, 2007). There are some excellent reviews by Calisto and Esteves (2009), Pal et al. (2010), and Santos et al. (2010).

Not surprisingly, antidepressants were among the myriad of pharmaceuticals detected at measureable concentrations. Historically, fluoxetine was the most commonly detected antidepressant in wastewater. Kolpin et al. (2002) measured fluoxetine at 0.012 μg/L downstream from wastewater treatment plants and from livestock production facilities in the United States. Their study was one of the first large scale studies of API contamination in North America. However, their measured concentrations for fluoxetine were lower than those reported by Weston et al. (2001) of from 0.32 to 0.54 μg/L in municipal effluent and surface waters and 0.509 μg/L in Canadian wastewater effluent (Chen et al., 2006).

Sertraline is the active ingredient in the antidepressant Zoloft and is one of the most commonly prescribed antidepressants in the world (Schultz et al., 2010). It has been measured at concentrations similar to fluoxetine. The highest environmental concentrations of sertraline measured to date have been reported from raw sewage in Norway at 0.0084 μg/L Vasskog et al. (2006), in Canada at 0.006 μg/L and in Canadian effluent at 0.005 μg/L (Lajeunesse et al., 2008).

In recent years, the SSNRI venlafaxine and SSRI citalopram have surpassed fluoxetine as the antidepressant occurring in the highest environmental concentrations. These antidepressants have been measured at concentrations up to 10X higher than any for fluoxetine. Lajeunesse et al. (2008) measured venlafaxine concentrations from Canadian treatment plants of from 0.195 to 0.213 μg/L in raw sewage, 0.176–0.214 μg/L in effluent and 0.013–0.045 μg/L in receiving streams flowing into the St. Lawrence River. In the same year Schultz and Furlong (2008) measured venlafaxine at 2.19 μg/L in wastewater effluent in Minnesota and at 1.31 μg/L downstream from treatment plants in Texas. These are the highest environmental concentrations reported for any antidepressant. Later, Schultz et al. (2010) published mean concentrations of venlafaxine from Boulder Creek, Colorado as high as 0.22 μg/L. Metcalfe et al. (2010) measured mean concentrations of venlafaxine > 1.0 μg/L in raw wastewater and 0.5 μg/L at sampling sites 10 m downstream from the treatment plant in the Grand River watershed of southern Ontario.

For citalopram, Lajeunesse et al. (2008) reported concentrations of 0.052 μg/L in raw sewage, 0.057 μg/L in effluent, and 0.011 μg/L in receiving water. It has been measured as high as 0.07 μg/L in American wastewater effluent by Schultz et al. (2010). Metcalfe et al. (2010) reported higher mean concentrations of citalopram in raw Canadian wastewater (approximately 0.25 μg/L) and 10 m downstream (approximately 0.125 μg/L). Styrishave et al. (2011) measured concentrations of citalopram in raw wastewater from 0.19 to 10.3 μg/L in a Danish treatment plant.

In the marine and estuarine environment, reports of measured concentrations of SSRIs are few. Fluoxetine was detected once in the southern portion of the Chesapeake Bay at a concentration of 0.003 μg/L (Pait et al., 2006). Fluoxetine was detected by Benotti and Brownawell (2007) in wastewater influent at 600 (±280) ng/L and in effluent at 560 (±250) ng/L in Jamaica Bay, New York.

While the antidepressants mentioned above are indicated for the treatment of anxiety, panic disorder, and obsessive-compulsive disorder to name a few, and all work by modulation of the neurotransmitters serotonin, dopamine, and norepinephrine at the pre-synaptic terminal, these drugs can have multiple biological effects in humans such as weight gain, fatigue, and sexual dysfunction. Furthermore, since the genes for the reuptake transporters and/or receptors undoubtedly evolved in invertebrates such as molluscs and crustaceans, and quite possibly even in plants (e.g. serotonin and dopamine are both widely distributed in plants, Udenfriend et al., 1959), release of drugs designed to modulate evolutionarily ancient neurotransmitters would be expected to have multiple biological effects on these organisms.

2. Overview of neurohormones impacted by antidepressants

2.1. Mollusca

A thorough review of the roles of neurohormones in the regulation of physiological and behavioral mechanisms in molluscs encompasses research from more than 50 years ago, and thus goes well beyond the scope of this paper. We present here a cursory look at some of the physiological systems that are regulated by two principal biogenic monoamines, serotonin and dopamine. There are excellent reviews by Weiger (1997) (on behavior), Dayan and Huys (2009); Wu and Cooper (2012) (on receptors and synaptic

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