**Background**

Global climate change and other human influences are already impacting natural aquatic environments and are expected to increase in intensity in the coming decades. These diverse changes include input of pollutants into waterways, altered river flow that can affect water chemistry and hydrography, sea level rise, increasing intensity of temperature fluctuations and overall temperature rise, and decreasing ocean pH. The marine environment, especially in nearshore areas, is already hypervariable, home to inherent stressors for marine organisms. As the environment continues to change, local populations will either have to adapt to new sources of environmental variability and weather new stressors, or they will be forced to shift their ranges to more suitable habitats. In this way, both the ecology and biology of aquatic animals can give us insight into the kinds of changes that are occurring in the marine environment, as well as how those changes are affecting organism physiology and fitness. Sessile marine organisms are especially useful in this regard since they serve as environmental sentinels for a specific location.

*In situ* experiments, such as biomonitoring, give insight into how a specific location’s environment impacts local populations; however, controlled laboratory exposures can provide greater information on specific responses to targeted stressors. In a laboratory setting, dose-dependent responses can also be more easily established (e.g. Lüchmann et al., 2011). This precise information can then be applied in a field context to better understand to which environmental changes organisms are reacting.

Pacific oysters, *Crassostrea gigas*, have a long history as subjects of ecological, physiological, and molecular research, making them a strong model for further explorations of response to environmental change. *C. gigas* is a dioecious broadcast spawner that inhabits the intertidal environment, which is subject to daily, seasonal, and annual environmental fluctuations. Pacific oysters have also been introduced for aquaculture worldwide, proving adept at inhabiting a variety of environments and even out-competing some local species. These ecological and biological characteristics suggest that *C. gigas* is well adapted to environmental change, at least the natural sources of change that it has encountered to this point. As such, it is a robust physiological model in which to study the effects of environmental extremes.

**Ocean acidification**

Ocean acidification is the reduction of ocean water pH due directly to rising levels of atmospheric CO2. Since the industrial revolution in the 18th century, CO2 deposition into the atmospheric has increased at an accelerating rate. The increasing partial pressure of CO2 (*p*CO2), as well as other greenhouse gases, has contributed to what is commonly known as global warming, as well as ocean acidification. Current average atmospheric *p*CO2 is approximately 400 ppm, higher than the highest *p*CO2 over the past 2.1 million years (approximately 300 ppm; Hönisch et al. 2009). According to the Intergovernmental Panel on Climate Change’s (IPCC) B1 scenario (stabilized population growth by 2050 and a more service- and information–driven economy), average global CO2 emissions will attain 650 ppm by 2100 (Caldeira and Wickett 2005). If population growth occurs at a higher rate accompanied by slow economic development and limited technological changes (IPCC’s A2 scenario), emissions will likely reach 970 ppm by 2100 (Caldeira and Wickett 2005). The atmospheric *p*CO2 increases that have already occurred have caused a global trend of the undersaturation horizon of CaCO3 moving up to more shallow waters (Feely et al., 2004, 2012), which is projected to become more persistent and widespread by 2050 and beyond (Gruber et al., 2012).

*Chemistry*

The reduction in pH from atmospheric CO2 equilibration with ocean water occurs according to the following reaction:

CO2 + H2O  H2CO3  H+ + HCO3-  H+ + CO32-

The thermodynamic equilibrium of the reaction favors the production of bicarbonate (HCO3-) and hydrogen ions (H+), and results in a lower saturation state (Ω) for carbonate ion (CO32-). Since pH is negatively correlated with concentration of H+ in solution, this reaction is directly responsible for lower oceanic pH. Additionally, the lower Ω creates a less favorable environment for maintaining and creating calcified structures.

Certain ions in ocean water are contributors to total alkalinity (AT), which can be considered as a buffering capacity for changes in pH. Total alkalinity represents a balance between H+ donors and acceptors in water and the greater AT in a body of water, the greater its ability to mitigate changes in pH. Thus, different geographic areas with different AT – which can change according to riverine inputs, biological activity, weathering of rocks, etc. – will experience different degrees of ocean acidification. On a global scale, however, the trend is towards lower pH. The equilibration of anthropogenic CO2 is increasing the total inorganic carbon (DIC) shifting the relative amounts DIC and AT and contributing to CaCO3 undersaturated waters at shallower depths (Feely et al., 2004, 2012). Changes in AT based on the natural global carbon cycle (i.e. input from weathering on continents and removal through burial in ocean sediment) occur on the scale of thousands of years (Zeebe, 2012), much longer than the current carbonate chemistry changes. Additionally, elevated *p*CO2 can change the buffering capacities of estuarine areas where fresh river water flows into the ocean (Hu and Cai, 2013). Due to the current accelerated timescale of CO2 input into the oceans, pH changes will continue largely unchecked by natural processes that have moderated fluctuations in the past.

*Nearshore environmental processes*

Oceanic pH is affected by many other processes in addition to atmospheric *p*CO2. Especially in the relatively shallow and productive nearshore environment, many physical and biological processes contribute to fluctuations in pH on a variety of timescales (i.e. Booth et al., 2012). In upwelling zones along the coast, cold, CO2-rich water can be pulled into productive areas as surface water is displaced. Upwelling represents a relatively transient yet strong signal in terms of pH fluctuations. In the California Current System, upwelling events bring water with aragonite saturation state of less than 2 into the nearshore environment for most of the spring, summer, and fall (Plattner et al. 2009). Greenhouse gases cause land masses to warm more than the ocean, creating a low pressure cell over coastal areas. These low pressure cells increase wind strength and upwelling intensity, thereby augmenting a global trend towards winds favoring upwelling conditions (Bakun et al., 2010). Local hatcheries on the Pacific coast of the United States have linked larval mortalities and decreased production with upwelling events (Barton et al., 2012) and have consequently changed their hatchery practices to avoid upwelled water.

The relatively high productivity of nearshore environments can lead to a strong CO2 signal from respiration and photosynthesis occurring on a more short-term cycle (daily to seasonal). Photosynthesis, respiration, and calcification can change absolute and relative amounts of CO2 species (Smith and Key, 1975). Photosynthesis and calcification decrease the amounts of CO2 in seawater while respiration and dissolution of calcified structures increase CO2 (Smith and Key, 1975). Since upwelled waters typically contain high amounts of nutrients they tend to stimulate production in the nearshore environment. During upwelling, changes in nearshore DIC occur mostly from organic matter production and respiration and CaCO3 dissolution (Fassbender et al., 2011). As anthropogenic carbon inputs change the baseline of *p*CO2 in seawater, these natural processes could contribute to making the overall *p*CO2 even lower than predicted.

*Ocean acidification in Puget Sound*

Puget Sound, WA and other similar bodies of water have hydrographies that contribute to variability in pH. Puget Sound is a semi-enclosed, urban estuary bordered by approximately 4.1 million people (U.S. Census Bureau, 2012 estimates). Puget Sound is subject to low transport/high water residence times in some basins (Babson et al., 2006), which can exacerbate low pH and low oxygen events. This pattern of hydrography results in relatively shallow low pH events in the summer months, especially in southern Hood Canal where the longest residence times are found (Feely et al., 2010). The major contributors to these pH fluctuations are natural processes, however elevated atmospheric *p*CO2 has also contributed to an overall decrease in pH in the Sound (Feely et al., 2010).

**Implications for bivalves**

Bivalves and many other aquatic invertebrates have proven to be sensitive to acute exposures to elevated *p*CO2 across life stages. It is difficult to make direct comparisons across studies due to differences in exposure time, *p*CO2 level, and, most importantly, ecological and evolutionary history of exposure to low pH events for the source population of study (i.e. Kelly et al., 2013; Parker et al., 2012). However, generalities of the effects of ocean acidification on bivalves do emerge from these studies.

Bivalve larvae are more sensitive to changes in water chemistry than juveniles and adults, perhaps due to the energetic demands of early growth, calcification, and metamorphosis. At the phenotypic level, growth and calcification of bivalve larvae are negatively impacted by elevated *p*CO2 (Barros et al., 2013; Barton et al., 2012; Gaylord et al., 2011; Hettinger et al., 2012; Kurihara et al., 2007; Miller et al., 2009; Parker et al., 2010; Talmage and Gobler, 2011; Waldbusser et al., 2010). These phenotypic changes likely result from changes in energetic resource allocation in the larvae since they are manifested around the time when larvae make the transition from endogenous, maternally provided energetic resources to exogenous food (Barros et al., 2013; Barton et al., 2012; Timmins-Schiffman et al., 2012). The extra energetic demand of dependence upon external food resources means that fewer resources are available for other processes, such as growth and calcification, resulting in an overall developmental delay in ocean acidification-exposed larvae.

Around the same time as this metabolic shift, early larvae are beginning the process of calcification, which is more energetically demanding at the D-hinge stage than at later stages (Waldbusser et al., 2013). D-hinge larvae have higher amounts of seawater-derived carbon in their precipitated shell, suggesting that either they are unable to fully isolate their calcifying space or they require relatively more DIC than later stage larvae (Waldbusser et al., 2013). Either hypothesis would mean that early stage calcification is highly sensitive to changes in carbon availability (i.e. CaCO3 saturation state). The precise mechanisms behind developmental delay and other changes observed in bivalve larvae have yet to be fully characterized, but a proteomic investigation of *Crassostrea hongkongensis* larvae exposed to elevated *p*CO2 revealed that ocean acidification causes a down-regulation of proteins involved in metabolic pathways (Dineshram et al., 2013).

Adult bivalves are generally less sensitive to changes in oceanic *p*CO2, but still exhibit changes in growth, calcification, and many important physiological processes in response to ocean acidification. Bivalve shell deposition is negatively impacted by elevated *p*CO2 (Gazeau et al., 2007) and some studies have illustrated decreased shell growth in low pH-exposed juveniles and adults (Beniash et al., 2010; Michaelidis et al., 2005; Thomsen and Melzner, 2010). The negative effects of decreased pH (and thereby decreased Ω) are most often manifested in weaker shells that are structurally compromised (Dickinson et al., 2012; Dickinson et al., 2013; Welladsen et al., 2010).

A range of other physiological processes have also been explored in the adult bivalve response to ocean acidification, illustrating the wide-ranging effects of this environmental stress. Changes in metabolic processes may change the energetic resources available for other physiological processes. In *C. virginica*, glycogen and lipid in whole body tissue decreased after an eleven week exposure to low pH (Dickinson et al., 2012). Similarly, metabolic shifts were evidenced in *C. gigas* after a 55-day exposure to low pH by changes in metabolites in the mantle and gill tissue (Lannig et al., 2010). During concurrent exposure to elevated temperature and ocean acidification, *C. gigas* increased metabolic usage of carbohydrates and lipids compared to proteins (Clark et al., 2013). The important impacts of ocean acidification on metabolic processes is further evidenced by studies that have revealed that the negative effects of elevated *p*CO2 are largely mitigated when mussels have greater access to food resources (Melzner et al., 2011; Thomsen et al., 2013).

Bivalve hemolymph pH closely tracks environmental pH (Lannig et al., 2010; Thomsen et al., 2013). The change in hemolymph pH may be the main contributing factor to changes in bivalve immune parameters during exposure to elevated *p*CO2. Short-term ocean acidification exposure coupled with elevated temperature altered hemocyte parameters in the clam *Chamela gallina* and the mussel *Mytilus galloprovincialis* (Matozzo et al., 2012). There is also evidence of increased oxidative stress in bivalves at the cellular (Matoo et al., 2013), gene expression (Clark et al., 2013), and protein expression levels (Tomanek et al., 2011).

**Applying Molecular Tools to Study Environmental Change**

Molecular ecology is the use of molecular data (i.e. DNA, RNA, or protein) to explore interactions between organisms and their environment. These tools can be applied at the individual gene or protein level (targeted gene sequencing, qPCR, or Western blots) or on a global scale (genomics, transcriptomics, or proteomics). The latter is a non-biased approach in which the organism is assayed for its response to the environment and can be the basis for discovery of complex organism-environment interactions and biomarker development.

Genome sequencing can provide information on the genomic resources possessed by a species as well as insight into adaptation and evolution. The recent sequencing of the *C. gigas* genome revealed that oysters have an expanded repertoire of stress response genes compared to the genomes of seven other species (Zhang et al., 2012). Similarly, the *Daphnia pulex* genome possesses expanded gene families for photoreactive/photoresponsive genes as well as high rates of gene duplication that could provide the basis for responding quickly to environmental changes (Colbourne et al., 2011).

Transcriptomics, or high throughput sequencing of mRNA, can also illustrate evolutionary-scale changes since single nucleotide polymorphisms (SNP) are found at the DNA and mRNA levels. SNP frequency data at the transcriptomic level were used to evidence an adaptive response of sea urchin larvae to elevated *p*CO2, specifically in genes involved in lipid metabolism, ion homeostasis, cell signaling, and protein modifications (Pespeni et al., 2013). Gene expression data can also elucidate functional molecular responses to an environmental change. In *C. gigas*, transcriptomic sequencing revealed that the oyster transcriptomic response to elevated *p*CO2 differed between different temperatures (Clark et al., 2013).

Lastly, proteomics provide insight into the truly functional changes that occur at the molecular level in response to different habitats or environmental change. Proteins are functional molecules that effect changes at the phenotypic level (whereas changes in gene expression may not always translate into changes in protein expression). Proteomics have been used to reveal physiological changes that underlie adaptation to different environmental salinities in European whitefish (Papakostas et al., 2012), proteins that are associated with specific behavioral traits in the honey bee (R. Parker et al., 2012), as well as general changes in overall protein expression in response to a specific environmental stress (Dineshram et al., 2013; Jones et al., 2013; Letendre et al., 2011; Malécot et al., 2013; Parker et al., 2011; Tomanek et al., 2011; Wong et al., 2011). Changes in post-translational modifications (specifically phosphorylation status), which also play a role in whether or not a protein is expressed, can also be investigated using phosphoproteomics (e.g. Dineshram et al., 2013; Li et al., 2013).

This dissertation explores the effects of ocean acidification on the Pacific oyster, *Crassostrea gigas*, at two different life stages. In the first chapter, larvae are exposed to elevated *p*CO2 to assess how ocean acidification affects the earliest stages of development. Chapter two describes the development of shotgun proteomics tools that can facilitate the study of the mechanisms behind the oyster’s response to ocean acidification and other environmental stressors. Chapter three details the effects of ocean acidification on the adult oyster proteomic response, fatty acid profiles, shell deposition, and response to another stressor. Lastly, Appendix A is an investigation of specific antioxidant response enzymes and their role in the response to elevated *p*CO2. The work as a whole represents novel investigations into the mechanisms behind the invertebrate response to elevated *p*CO2. By combining analyses across different life stages and different scales (i.e. molecular to phenotypic), and the results illustrate the integrative response of oysters to this environmental stress.

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