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Potential Synergism between Stress and Contaminants in Free-ranging Cetaceans

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Noise has increased significantly over the last decades in oceans, and this trend is accelerating in large part because of oil exploration and exploitation, both of which are expanding worldwide. Considered together with recent evidence that noise disturbs the behavior, echolocation, navigation and communication of marine mammals, it is likely that noise, increasingly encountered by marine mammals, will add to their allostatic load. Glucocorticoids (GCs) are the major hormones that mediate the long term effects of stress. GCs' effects depend, among other factors, on the intracellular concentrations of the various isoforms of the glucocorticoid receptors (GR). Tissue and cell-type specificity are also conferred by the presence in target cells of GR ligands such as chaperones, co-chaperones and modulatory element binding proteins whose concentrations vary according to tissue, cell types and even to the cell cycle phase. The normal regulation of GCs production in adult life relies on the normal development of the hypothalamus-pituitary adrenal (HPA) axis in uterine and early postnatal life, which in turn depends on the absence of chronic stress imposed to both the mother and newborn during these critical periods. Worldwide, cetacean populations, such as the beluga population inhabiting the St Lawrence Estuary (SLE) in Canada, are exposed to anthropogenic stressors, and are contaminated by persistent lipophilic contaminants of which many are abundantly transferred to newborns during lactation. GCs and certain organochlorine contaminants (OCs), for instance dioxin-related polychlorinated biphenyls (DRPBs), mediate their prolonged and profound effects through nuclear receptors such as aryl hydrocarbon receptors (AhR). These effects are exerted on most organs, especially on the developing brain and lymphoid organs of fetuses and juveniles and on adrenal glands of adult mammals. Multiple interactions have been demonstrated between GCs and OCs, often through interactions between their receptors. These interactions may disturb the delicate balance required by immature and adult mammals to react optimally to stressors.

Stressors elicit a fairly stereotyped response in higher vertebrates, including marine mammals. In general, the elevation of circulating GCs levels that follows exposure to various stressors – including noise - is beneficial. High GC levels become detrimental however when they occur over a long period, when the stressor is persistent or repeated (Deak, this issue; Romero & Butler, this issue; Sapolsky, Romero, & Munck, 2000; St. Aubin, De Guise, Richard, Smith, & Geraci, 2001; St Aubin & Dierauf, 2001).

The sympathetic nervous system (SNS) responds within seconds to stressors by releasing preformed catecholamines (CAs) (epinephrine and norepinephrine) from the adrenal medulla into the blood circulation. This release quickly increases heart rate and blood pressure, which is part of the acute - or fight or flight – response. These effects occur within seconds because CAs bind adrenergic receptors present in peripheral tissues. The binding triggers an

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immediate intracellular biochemical cascade through secondary messengers (Romero & Butler, this issue). When extreme, this response may kill animals and humans through CAs' toxic effects on heart muscle fibers (McEwen, 1998, 2000). In addition, within several minutes, CAs induce the production of T helper cells (Th)-1, proinflammatory (or cell-mediated immunity) cytokines (see below), probably to prepare the organism to fight bacterial invasions secondary to potential wounds.

Concurrently with CA release, hypothalamic neurons trigger indirectly the release of GCs from the adrenal glands. Hypothalamic neurons first signal the pituitary to release ACTH via the corticotrophin releasing hormone (CRH). In turn and within minutes, ACTH triggers the synthesis and release of GCs from the adrenal cortex where GCs are synthesized from cholesterol (hence their lipophilicity). GCs are then distributed indiscriminately throughout the stressed organism, and traverse the lipid-based cytoplasmic membranes of most cells. This broad distribution explains in part GCs' impact on a wide variety of cells. Each cell type, including inner ear cells (cochlea, organ of Corti), is distinguished by the presence of various isoforms of intracytoplasmic GR and other GC ligands such as chaperones, co-chaperones, and modulatory element binding proteins (heat shock protein 90 (hsp 90), immunophilins and GMEB-1 respectively), ensuring that GCs' effects are tissue and cell type specific (Canlon, Meltser, Johansson, & Tahera, 2007; De Bosscher, Vanden Berghe, & Haegeman, 2002; Horner, 2003). Elevated GC levels elicited by acute stress repress the CA-induced production of proinflammatory cytokine by Th1 cells through GR. The present review will address the potential interactions between contaminants, stress and the immune system in marine mammals at the molecular level. It will not deal with the possible role of stress on the high cancer rates seen in some populations of marine mammals (Martineau et al., 2002). The latter will be addressed elsewhere (Martineau, in preparation).

Immune system: A review

The immune system is classically divided in two major branches, innate and adaptive. The innate branch, constantly in standby alert to defend the body against microorganisms or trauma, is not antigen (Ag)-specific, and has no memory of previous encounters with microorganisms, e.g. it reacts the same way regardless of the number or extent of previous encounters. Most of those microorganisms that invade the body are quickly eliminated by the members of the innate system, monocytes/macrophages, neutrophils and natural killer (NK) cells, through acute inflammation. Acute inflammation is characterized by increased vascular permeability resulting of the action of histamine and bradykinin, but also of interleukin (IL)-1 and Tumor Necrosis Factor alpha (TNF-α). The latter two molecules, "IL-1-like cytokines", are produced by local macrophages, and are major actors of inflammation, for which they are called proinflammatory cytokines. IL-1-like cytokines also induce the expression of adhesion molecules by endothelium used by neutrophils to adhere to the walls of capillaries adjacent to inflamed sites. Interleukin (IL)-8, a molecule also synthesized by endothelial cells,

has complex effects on neutrophils, resulting in their firm adhesion to vascular walls and sequestration at the inflammatory site. Then neutrophils traverse these walls to migrate into damaged tissues which become infiltrated – and destroyed – by large numbers of neutrophils.

If acute inflammation cannot eliminate the aggressing microorganism, and/or if damages are too heavy, chronic inflammation ensues after several days. Neutrophils are progressively replaced by extensive numbers of monocytes/macrophages which engulf and kill microorganisms, and clean up tissue debris. Lymphocytes and fibroblasts accompany macrophages (fibroblasts synthesize collagen, a major component of fibrous (scar) tissue).

Simultaneously, macrophages and dendritic cells (DC) (specialized macrophages), also produce IL-12, which triggers the production of interferon (IFN)-γ by lymphocytes. In turn, IFN-γ further increases the ability of macrophages to kill microorganisms. Macrophages start presenting antigens to $CD4^+$ naïve T cells, a lymphocyte subpopulation. The IL-1 and TNF-α produced by macrophages also activate these lymphocytes, thus launching the first steps of an immune response.

In contrast to the innate branch, the adaptive branch is antigen (Ag) specific and is endowed with memory, e.g. its cellular members (lymphocytes and their products) recognize a given Ag a long time after they first encounter it. Antigen presenting cells (APCs) e.g. macrophages, dendritic cells (DC) and B cells, phagocyte foreign invaders such as bacteria, and break them down into minute fragments which are physically presented on their surface to $CD4^+$ T cells. DCs are the most efficient APCs and the most important in activating lymphocytes. On the APC surface, the Ag is presented within a cleft of certain surface proteins called major histocompatibility complex (MHC) molecules. This encounter causes undifferentiated ($CD4^+$) T cells to produce one of two distinct cytokine patterns, Th1 or Th2. The Th1 pattern, generally seen as pro-inflammatory, is directed at intracellular invaders such as viruses and certain bacteria. The Th2 pattern, broadly considered as anti-inflammatory, is central to humoral immunity (or "antibody-mediated" immunity). Antibodies are most efficient at fighting extracellular parasites such as helminthes (ex.: nematodes, cestodes, trematodes) and most pathogenic bacteria.

Th1 and Th2 are mutually antagonistic. For instance, Th1 differentiation is inhibited by IL-4, the major Th2 cytokine involved in differentiating T cells into Th2 cells (IL-4 is produced by Th2 lymphocytes, mast cells and eosinophils). The severity of tissue destruction in an organ or at a particular anatomical site during an attack by a pathogenic agent is the result of the Th1/Th2 balance prevailing at that site (with a high ratio being synonymous of severe tissue damage). A third category of T cells (T reg) has a negative regulatory effect on both Th1 and Th2 cells by the production of transforming growth factor (TGF)-β.

Which pattern will be followed depends among other factors on the type of APC (there are many types of DC and macrophages), the nature of the presented Ag, and the local relative concentrations of other cytokines. The production of IL-12 by APCs, mostly by DC, plays a central role in the differentiation of T cells into Th1 cells. Th1 cells are responsible for cell-mediated immunity; they release

cytokines among which IL-2 is central for macrophages and cytotoxic T cells ($CD8^+$) activation. Cytotoxic T cells ($CD8^+$) are lymphocytes committed in killing otherwise normal host cells infected by viruses or intracellular bacteria and abnormal host cells such as tumor cells.

Th2 cells produce a battery of cytokines (IL-4, -5, -9 and -13) that help B cell differentiating into antibodies-(IgE) producing cells. Other cytokines involved in Th1 to Th2 differentiation include CCL1 (CC- chemokine ligand 1), which plays a role in cardiovascular diseases and allergic diseases such as asthma.

IFNs are an essential part of the innate system that participates also to the adaptive system, for instance by increasing MHC proteins expression. These molecules are released in the microenvironment where they have an effect on the cells that produce them (autocrine effect) as well as on adjacent cells (paracrine effect). All those cells become protected against viral infection (interferons *interfere* with viral infection) among other effects. IFNs are classified in two groups: type I group is composed of IFN α, β and ω, which are produced by almost all cell types mainly to protect against viral infection. Their expression is partially under the control of transcription factors nuclear factor kappa B (NF-κB), interferon regulator factors (IRF)-3 and other transcription factors (IRF-3 activation itself is triggered by viral infections). Reciprocally, the expression of type I IFNs leads to IRF-3 activation, resulting in a positive feedback loop (Jonasch & Haluska, 2001).

Type II IFNs are composed of a single member, IFNγ, which plays a central role in inducing the Th1 pattern. IFNγ is produced by APCs (among which DCs are the most important), Th1 cells and NK cells. Along with IL-12, IFNγ helps differentiating T cells into Th1 cells, and the latter in turn produce more IFNγ. As importantly, IFNγ activates macrophages in at least two ways: it enhances the capacity of macrophages to kill intracellular parasites, and triggers the production of IL-12, -6 and -18 by macrophages, which further increases Th1 differentiation.

. NF-κB is a family of five transcription factors: NF-κB1 (p105/p50), NF-κB2, RelA, RelB and c-Rel, all involved in inflammation. All members form homo- or heterodimers which repress or activate the expression of a plethora of mammalian pro-inflammatory genes such as IL-1, -2, -4, -8, -12, IL-2R, and others. NF-κB1 and NF-κB2 homodimers decrease the transcription of these pro-inflammatory genes whereas RelA and RelB activate it. NF-κB members are implicated in IL-12 expression by APC, and thus are essential to Th1 differentiation. They also play a central role in innate immunity, inflammation and infection, suppression of lymphocyte apoptosis (programmed death), and DC development **(**Caamaño & Hunter, 2002). Inactive NF-κB lies in the cytosol bound to IκB, an inhibitor. Various factors such as cytokines and growth factors, or cellular stresses such as bacteria and viruses, trigger the phosphorylation of IκB, which then releases NF-κB. The latter translocates to the nucleus where, like GR and the AhR, it recognizes specific DNA sequences, appropriately named κB sequences.

Glucocorticoid receptor

GC-mediated GR activation accounts for the anti-inflammatory effects of GCs. Activated GR blocks the expression of all pro-inflammatory cytokines such as IL-1 and Th1 cytokines, leaving intact the production of "anti-inflammatory" Th2 cytokines. Thus GCs protect cells and tissues from damages inflicted by exaggerated cell-mediated Th1-type immune response (Ramirez, Fowell, Puclavec, Simmonds, & Mason, 1996; Sapolsky et al., 2000). Liganded GR also activates the transcription of anti-inflammatory proteins such as Clara cell protein 10, IL-1 receptor antagonist, lipocortin, mitogen-activated protein kinase phosphatase-1, neural endopeptidase, and serum leukoprotease inhibitor. Liganded GR activates these genes by binding DNA, specifically the GRE sequences located in the regions that control the expression of these genes.

GR-mediated repression of Th1 functions is mainly exerted through transcriptional repression of at least three pro-inflammatory transcription factors, NF-κB, IRF-3, and AP-1 (the latter is a complex made of two nuclear molecules, c-fos and c-jun). The liganded GR represses the transcription of these factors by protein-protein interactions, not by binding DNA elements. Most of these anti-inflammatory effects are mediated by interactions between liganded GR α and NF-κB. It has been hypothesized that NF-κB may compete with GR for coactivator molecules necessary for the transcription of genes targeted by both activated GR and NF-κB. These two coactivators, "Steroid receptor coactivator-1" (SRC-1) and "p300/CBP", are responsible for making gene promoters accessible to the transcription machinery by acetylating histones. Importantly, SRC-1 and p300/CBP also bind the AhR, a cellular receptor which mediates the toxicity of many contaminants. In addition, p300/CBP also binds IRF-3, suggesting that competition for coactivators could occur between GR, NF-κB and AhR (Smoak & Cidlowski, 2004; Tian, Rabson, & Gallo, 2002). IRF-3 augments IFN α and β transcription and also elevates the transcription of other pro-inflammatory genes such as Il-15 and RANTES, a chemoattractant of eosinophils and monocytes (Hiscott et al., 1999; Taniguchi, Ogasawara, Takaoka, & Tanaka, 2001). The activated GR becomes tethered to DNA-bound IRF-3, and inhibits the transcription of IRF-3 target genes (Kassel & Herrlich, 2007).

Elevation of GC circulating levels prior to exposure to loud noise protects the inner ear from audiogenic trauma and conversely, a failure to elevate GC levels prior to or during audiogenic trauma increases damages (Canlon et al., 2007). In contrast, chronic stress, which results from repeated or prolonged exposure to a stressor and leads to prolonged adrenocortical stimulation by ACTH and exposure to high GC levels, has deleterious effects on most organs, especially on the brain and the immune system (Table 1) (McEwen, 1998; Sapolsky et al., 2000; Romero & Butler, this issue). Note that sustained high levels of ACTH are correlated morphologically with hyperplasia and hypertrophy of the adrenal cortex (Ulrich-Lai et al., 2006). For instance, suicide victims, patients suffering depression and captive non human primates exposed to social stress all show an increase of adrenal mass due to chronic stress (Swaab, Bao, & Lucassen, 2005).

Table 1
Similarities between glucocorticoid receptor (GR) and aryl hydrocarbon receptor (AhR).

Characteristic	GR	AhR	Reference
Function	Nuclear receptor for endogenous hormone, glucocorticoid (released under physiological stress).	Nuclear receptor for xenobiotic. Regulate (enhance) exogenous compound metabolism.	Hahn, 2002; Escriva, Safi, Hänni, et al., 1997; Tian et al., 2002.
	Important for development		
Intracellular location	Intracytoplasmic. Ligand- activated migration to nucleus		
Constitutive ligand	hsp90		
Ligand hydrophobicity	Hydrophobic		
Other ligands	NF-κB		
Target sequence	GRE	DRE (dioxin responsive element) or Xenobiotic responsive element (XRE)	
Natural endogenous ligands	Glucocorticoids	Unknown	
Targets	Multiorgans		
Effects timescale	Prolonged		
Major immune cells targets	T cells		
Selected effects of long term ligand-mediated activation	Immune suppression (T-cell apoptosis and decreased thymus development)	T cells, B cells, dendritic cells	Kerkvliet, 2002
	CYP induction		Herold, McPherson, & Reichardt, 2006. McMillan, McMillan, Glover, et al., 2007.
	Neurotoxicity		Hahn, 2002; Wang, Faucette, Gilbert et al., 2003.
	Diabetogenic		De Kloet, Vreugdenhil, Oitzl et al., 1998; Williamson, Gasiewicz, & Opanashuk, 2005.
			Buckingham, 2006; Remillard & Bunce 2002; Matsumara, 1995.

Stress in cetaceans

Most studies carried out on captured cetaceans to measure stress-induced elevation of GCs suffer drawbacks, some of which are inherent to cetaceans: basal cortisol values are low, interindividual variations are wide, and increases in cortisol levels following stress exposure are lower than those seen in terrestrial mammals. Other drawbacks are inherent to wildlife studies: a long interval may elapse between chase/capture and sampling time, which makes difficult determining basal cortisol levels (Bossart, Reidarson, Dierauf, & Duffield , 2001; Ortiz & Worthy, 2000; St. Aubin et al., 2001; St Aubin, 2001; St Aubin & Dierauf, 2001; St Aubin, 2002 a, b). In spite of these problems, elevated cortisol levels have been associated with stressors in marine mammals and in Eastern Tropical Pacific (ETP) dolphins which are captured after the intensive chase involved in tuna fishing (Bossart et al., 2001; St. Aubin, Ridgway, Wells, & Rhinehart, 1996; St Aubin, 2002 a, b). Chased ETP dolphins showed typical evidences of acute stress such as elevated circulating GC levels, high circulating levels of glucose, decreased circulating levels of iron, thyroid hormone levels, and the presence of a typical "stress leukogram" (increased number of circulating white blood cells due to neutrophils, and decreased numbers of lymphocytes and eosinophils). Other evidences of acute stress seen in these animals were clearly deleterious, such as the observed necrosis of cardiac muscle fibers, probably due to catecholamine overload (Cowan & Curry, 2002; St. Aubin, 2002 a, b).

In porpoises (*Pocoena phocoena*), Th1 proinflammatory cytokines levels were lower and cortisol levels were higher in accidentally captured animals than in captive animals. This difference was consistent with the switch from the Th1 proinflammatory to the immunosuppressive Th2 cytokine pattern seen in response to stressors (and high cortisol levels) in laboratory animals and humans (Fonfara, Siebert, & Prange, 2007; Fonfara, Siebert, Prange, & Colijn, 2007).

Anthropogenic background noise has increased tremendously in oceans over the last decades because of increased maritime traffic and exploration for and exploitation of oil and natural gas. Cetaceans are sensitive to seismic air and waterguns used for these industrial activities (Finneran, Schlundt, Dear, Carder, & Ridgway, 2002). Papers presented in this issue and other studies indicate that both diffuse (e.g. background) and source noises impact the behavior, social communications and navigation of free-ranging cetaceans, and presumably cause stress in these animals (Aguilar Soto et al., 2006; Fair & Becker 2000; Finneran et al., 2002; Foote, Osborne, & Hoelzel, 2004; Hatch & Wright, this issue; Ridgway, et al., 2001; Schlundt, Finneran, Gardner, & Ridgway, 2000; Wright et al., this issue, b). Anthropogenic sound is likely to impact whales even in the deep ocean because it can be transported over thousands of miles, and even deep diving whales can be impacted because high hydrostatic pressures prevailing at great depth do not decrease the hearing acuity of whales (Ridgway et al., 2001). Whether high cortisol levels due to noise or to other stresses can protect whales' inner ear from noise-induced damage is of course highly speculative at this point.

Contaminants and immunosuppression in cetaceans

Some populations of cetaceans are severely affected by multiple anthropogenic stressors. Cetaceans are long lived animals which occupy top positions of the food chain, and whose body is composed of a high percentage of lipids. Thus, it is not surprising that lipophilic contaminants widespread in the food chain and resistant to metabolism accumulate at very high levels in the tissues of these animals. In addition, contaminant levels are often higher in juvenile animals than in adults because contaminants are transferred to newborns from females through cetaceans' lipid-rich milk (Hickie et al., 2000; Martineau, Béland, Desjardins, & Lagacé, l987).

The beluga whale population which inhabits the St Lawrence Estuary (SLE), Quebec, Canada, was severely reduced by hunting from about 7,800 in 1866 to a current estimate of 1,100 animals (Standard error = 300, 95 % confidence interval = 500-1,800) (Department of Fisheries and Oceans Canada, 2007). The population has failed to recover although hunting ended in 1979. Systemic examinations of stranded carcasses started in 1982 have shown that these animals are severely contaminated by lipophilic contaminants compared to Arctic beluga whales. Many of these compounds are known immunosuppressors that often target the adrenal glands, the final effectors of all stress responses (De Guise, Martineau, Béland, & Fournier, 1998; Letcher, Klasson-Wehler, & Bergman, 2000a; Letcher et al., 2000b; Martineau et al., l987; Martineau et al., 1988; Martineau et al., 2002; Martineau, Mikaelian, & Lapointe, 2003).

SLE beluga whales also suffer a variety of opportunistic infections and parasite infestations, suggesting that they are immunosuppressed. In marine mammals, contamination with DRPBs has long been associated with immunosuppression. DRPBs-induced immunosuppression has been suspected to play a role in making harbor seals (*Phoca vitulina*) more sensitive to phocine morbillivirus. These viruses killed more than 20,000 harbor seals in 1988 in the Baltic Sea. Significantly higher tissular concentrations of polychlorinated biphenyls (PCBs) were measured in striped dolphins (*Stenella coeruleoalba*) affected by the 1990-92 morbillivirus epizootic in the Mediterranean Sea, compared to concentrations observed in previous and later years. This difference led to the conclusion that DRPBs may have impaired the dolphins' immune response to the viral infection (Aguilar & Borrell, 1994). A similar association between morbilliviral infection and high OC tissular levels has been observed in common dolphins (*D. delphis ponticus*) from the Black Sea (Birkun et al., 1999).

Young harbor seals fed for 2.5 years with fish contaminated with DRPBs and other pollutants showed compromised immune functions when compared with a group of seals fed with less contaminated fish (reviewed in van Loveren, Ross, Osterhaus, & Vos, 2000). Harbour porpoises stranded in the UK showed a significant, positive association between PCB levels and the number of nematodes infecting them (Bull et al., 2006). In porpoises whose blubber showed total PCB concentration above 17 µg/g, total PCBs levels were significantly more elevated in animals dying of infectious diseases than in those dying from trauma. Below a 17 µg/g concentration, there was no correlation, suggesting that PCB-induced

immunosuppression increases the frequency of infectious diseases (Jepson et al., 2005). PCB concentrations in the SLE population are higher than this putative threshold.

Deficits in immune functions are difficult to evaluate directly in free-ranging cetaceans, largely owing to the problems associated with rapidly obtaining and processing samples in the field. A logical approach to show that the immune functions of a given population are impaired would be comparing its immune parameters to those of a control population less exposed to pollutants. Many factors render such a comparison difficult: populations unexposed to pollutants probably do not exist, the inaccessibility of some populations, which introduce variables in the time required to collect and process samples, the stress of capture, which triggers cortisol release, and genetic differences. An indirect approach - measuring a pollutant dose-response effect - allows avoiding these drawbacks. In free-ranging harbor seals, the ability of lymphocytes to proliferate when stimulated by mitogens was negatively correlated with PCB concentrations. In dolphins, increased concentrations of PCBs and DDT in blood were shown to be inversely correlated with lymphocyte responses (Lahvis et al., 1995). Another approach consists in measuring the *in vitro* response of immune cells from a presumably "normal" population to pollutants added in concentrations identical or similar to those found in the tissues of contaminated animals from the same species. The proliferative response of beluga lymphocytes to mitogens and their spontaneous proliferation are impaired *in vitro* by exposure to concentrations of p,p'-DDT and PCB 138 similar to those found in tissues of SLE beluga (PCB 138 is one of the most abundant PCB congeners present in SLE beluga tissues) (De Guise et al., 1998). Measurements of cytokine production by stimulated phocid (*Phoca vitulina*) lymphocytes similarly exposed *in vitro* to DRPBs and PAHs showed a decrease in IL-2 production, suggesting that DRPBs might impair one of the major very first steps of cell-mediated immune response (Neale, Kenny, Tjeerdema, & Gershwin, 2005).

Beluga and other marine mammals are contaminated with a complex mixture of PCB congeners, distinct compounds and their metabolites. Such mixtures affect not only lymphocyte functions but also phagocytic cells such as neutrophils and monocytes in humans, beluga and dolphins (Levin, Morsey, Mori, & De Guise, 2004; Levin, Morsey, Mori, Nambiar, & De Guise, 2005a, b; Mori, Morsey, Levin, Nambiar, & De Guise, 2006). *In vitro* exposure of phocid macrophages to PCB and PAH caused decreased IL-1β production (Neale et al., 2005).

Contaminants, cytokines and stress

Similarly to GCs' effects, DRPBs' effects are prolonged and are mediated through an intracytoplasmic receptor, the AhR, for which DRPBs have enormous affinity (Barouki, Coumoula, & Fernandez-Salgueroc, 2007) (Table 1). Similar to the GR, the AhR is widely distributed in many organs and cell types, and often has contradictory effects, depending on cell type and organ. Many of these effects are

mediated through AhR binding to NF-κB, which leads either to NF-κB activation or inhibition depending on cell type and previous cell stimulation.

Historically, the AhR was first described as a sensor of exogenous contaminants such as DRPBs and PAHs (Denison & Nagy, 2003). AhR binding to these contaminants triggers a complex cellular response resulting in increased expression of cytochrome P450 (CYP) enzymes, enzymes involved in the degradation of various endogenous and xenobiotic compounds. Like GRs, which are constantly exposed to endogenous GCs in most animals and humans, AhRs are constantly exposed to their ligands, DRPBs, because these compounds are now ubiquitous in the environment and in the tissues of animals and humans (Savouret, Berdeaux, & Casper, 2003).

In the absence of a ligand, the AhR, like the GR, rests inactive in the cytosol, bound to several proteins among which hsp90, the same ligand that binds the GR. Upon binding DRPBs, AhR dissociates from hsp90 and translocates to the nucleus, where, like the liganded GR, it binds a specific DNA sequence, the xenobiotic responsive element (XRE). The XRE is present within the promoters of multiple genes, among which CYP1A1 (Table 1). Intracytoplasmic CYP1A1 generates many highly reactive metabolites from benzo[a]pyrene (B[a]P) (these metabolites, not B[a]P *per se*, are responsible for the powerful carcinogenicity of B[a]P). Beluga and seal AhRs have been cloned, and both show a high affinity for DRPBs, comparable to that of mice strains susceptible to DRPB toxicity, and thus these species should show the same susceptibility to DRPBs toxicity (humans are less susceptible to dioxin toxicity than rodents because the human AhR shows a weaker affinity for DRPBs) (Jensen & Hahn, 2001; Kim, Hahn, Iwata, Tanabe, & Miyazaki, 2002). As demonstrated *in vivo* in laboratory rodents, AhR gene expression can be induced in presence of DRPBs. Consistent with this finding, a "dose-response" relation has been found in the livers of free-ranging contaminated Baikal seals: AhR mRNA levels were proportional to DRPBs tissue concentrations (Kim,et al., 2005).

Ligand-activated AhR can interfere with GCs' effects in many ways depending on cell type, tissue, species, and on the duration of DRPB exposure (Ruby, Leid, & Kerkvliet, 2002). In order to increase the transcription of their target genes, the AhR, GR and NF-κB must bind certain transcriptional coactivators and corepressors. Two AhR coactivators, SRC-1 and p300/CBP, also bind the GR. In addition, p300/CBP also binds IRF-3 (Servant, Grandvaux, & Hiscott, 2002; Smoak & Cidlowski, 2004; Swanson, 2002; Tian et al., 2002). Although competition between GR and NF-κB for these coactivators does not seem to be involved in NF-κB repression by GR, it is possible that, when a combination of stress, inflammation, viral infection and DRPBs occur[1], together AhR, GR and NF-κB compete for SRC-1 and p300/CBP and possibly for other transcription factors such as the GR interacting protein 1 (GRIP-1) (Kassel & Herrlich, 2007).

[1] The infection of DRBPs-contaminated cetaceans by viruses is well documented (Aguilar & Borrell, 1994; Kassel & Herrlich, 2007).

Through AhR binding, DRPBs affect macrophages, DCs, T and B cells, all actors central to innate and adaptive immunity. For instance, liganded AhR triggers the expression of pro-inflammatory cytokine genes in human macrophages, whereas it triggers apoptosis in T cells and DCs (Camacho, Singh, Hegde, Nagarkatti, & Nagarkatti, 2005; Ruby, Funatake, & Kerkvliet, 2004; Vogel, Sciullo, & Matsumara, 2007). All lymphoid organs, especially the thymus, are affected (thymus, spleen, lymph nodes). DRPBs affect B cells directly, and probably impair T cells both directly and indirectly. Dioxin exposure also results in the appearance of a T reg cell subpopulation in mice (Funatake, Marshall, Steppan, Mourich, & Kerkvliet, 2005). Together these perturbations explain that rodents experimentally intoxicated with dioxin are more susceptible to a wide variety of infectious agents.

DRPBs cause chronic inflammation (more specifically macrophage infiltration) in many organs probably because these compounds increase proinflammatory cytokines (Fan, Yan, Wood, Viluksela, & Rozman, 1997; Nyska et al., 2004; Pande, Moran, & Bradfield, 2005; Vogel et al., 2004; Vogel, Nishimura, Sciullo, Wong, & Matsumura, 2007a; Vogel, Sciullo, & Matsumura, 2007b). In primary human macrophages and in a human macrophage cell line, DRPBs increase the production of a battery of pro-inflammatory cytokines (IL-1β, B cell activating factor of the tumor necrosis factor family (BAFF), B lymphocyte chemoattractant (BLC), IRF3, CCL1, TNF-α, and IL-8) (Diaye et al., 2006; Vogel et al., 2004; Vogel et al., 2007a; b). In contrast, DRPBs seem to have severe negative effects on DCs. In mice primary DCs, dioxin decreases the nuclear translocation and binding to κB DNA sequences of NF-κB, leading to accelerated maturation and apoptosis (Ruby et al., 2004). It should be kept in mind that these experiments vary in many respects, among which the animal species, the cell type and the lack or presence of cytokine-mediated cell activation. For instance, Vogel, Sciullo, & Matsumara (2007b) used an unstimulated human macrophage cell line in which RelB and AhR cDNA were transfected, whereas in contrast, a non transfected DC line from mice, activated by TNF-α, was used by Ruby et al. (2002).

In marine mammals, DRBPs exposure seems to decrease IL-1 production by macrophages. Peripheral blood mononuclear cells (PBMC) (monocytes and lymphocytes isolated from blood) from 4 free-ranging harbor seals captured from the wild were exposed to PCB congener 169, a DRBP. This exposure significantly decreased IL1-β production. This result is in apparent contradiction with one of the above study where IL-1 β production was increased (Vogel et al., 2004). Again, many differences in the protocols used may explain this discrepancy. Firstly, no time course measurements were carried out in the seal study, e.g. phocid IL-1 was measured only after 4-hour incubation. Thus an increase in IL-1 levels would have been missed if it occurred 4 hours after exposure. This is a serious concern given that the increase in IL-1 production seen in human macrophages was detected 6 hours post exposure (Vogel et al., 2004). Secondly, the contaminant concentrations used in the two experiments were widely different: seals PBMCs were exposed to a 20-μM concentration of PCB congener 169 whereas the human macrophage cell line was exposed to 10-nM dioxin. Accounting for PCB 169 toxic equivalency

factor (0.01), phocid seal PBMCs were exposed to a dioxin toxicity level 20 times higher than that used for the human macrophages. Thirdly, PBMCs are composed of lymphocytes and monocytes. Thus decreased IL-1β production could have been due to Th1 activity by the lymphocytes present in the cell mixture because Th1 activity represses IL-1β production by macrophages. Fourth, PBMCs could have been impacted by the high plasma cortisol levels expected from capture especially considering that PBMC were isolated up to 8 h after capture (Neale et al., 2005). Finally variation in species susceptibility to dioxin toxicity may also contribute to these apparently conflicting results.

In wildlife, PCB-contaminated fish provided some of the first hints that GC and AhR cellular pathways are somewhat related. Upon capture, PCB-contaminated fish did not show the expected elevated cortisol levels that capture normally triggers in noncontaminated fish (Hontela, Rasmussen, Audet, & Chevalier, 1992; Hontela, 2005). Recent experiments carried out in fish have provided mechanistic explanations for these early observations. In contaminated fish, AhR activation decreases GC synthesis by inhibiting two key proteins involved in two rate-limiting steps of the GC synthesis, first the steroidogenic acute regulatory protein (StAR), which transports cholesterol to the mitochondrial inner membrane and second, the cholesterol side chain cleavage (P450scc or CYP11A1/scc) enzyme, which converts cholesterol to pregnenolone, the first step of cortisol synthesis. In other words, AhR-ligand contaminants hamper one of the major adaptive responses to stress. Considering that both cortisol synthesis pathways and proteins involved in GC synthesis are highly conserved in animals, most likely these findings can be applied to higher vertebrates (Aluru & Vijayan, 2006). DRPBs metabolites can also bind the GR, competing with endogenous GCs and inhibiting GC synthesis (Brandt, Joensson, & Lund, 1992; Durham & Brouwer, 1990; Johansson, Nilsson, & Lund, 1998). Moreover AhR also mediates the endocrine disruption associated with DRPBs toxicity: among other effects, liganded AhR triggers the destruction of the estrogen and androgen receptors (ER and AR) through ligation with ubiquitin (Ohtake et al., 2007). The ER, AR and GR are all members of the superfamily of nuclear hormone receptors because of the many structural and functional similarities they share. For instance, in prostate cancer patient, an AR double mutant could bind cortisol (Zhao et al., 2000). Because of these similarities, it is possible that AhR also causes GR degradation.

DRPBs adrenal toxicity

Many OCs and their metabolites also severely damage the adrenal glands, the final effector organs of stress. There are several reasons why adrenal glands are vulnerable to these compounds. The vascular supply of the adrenal cortex is disproportionately large compared to the adrenals' mass. In addition, the adrenal cortex is rich in both lipids and CYP enzymes because it synthesizes steroids from cholesterol, which explains why adrenals accumulate high concentrations of lipophilic contaminants, which are then metabolized into more toxic molecules by the CYP enzymes (Harvey & Everett, 2003).

Degenerative and proliferative changes consistent with chronic stress and DRPBs intoxication are commonly observed in the adrenal cortex and medulla of SLE and Western Hudson Bay beluga whales and the severity of these lesions increases with age in both populations. The younger age of much less contaminated control beluga whales sampled from Hudson Bay precluded a comparison of lesion severity and prevalence between age-matched groups (Lair et al., 1997).

According to existing reports, adrenocortical cysts are rare in marine mammals except in SLE beluga and white-sided dolphins (Geraci & St. Aubin, 1979; Lair et al., 1997). In white-sided dolphins, these lesions were attributed to sinusoidal blockage or hypersecretion, and were considered associated with stress related with reproductive functions since 100 % of females and only 20 % of males were affected. No lesions have been observed in the adrenal glands of other Odontocetes species beside increased medullary and/or cortical mass in Atlantic bottlenose dolphins (*Tursiops truncatus*) and harbour porpoises (*Phocoena phocoena*) with chronic stress (Clark, Cowan, & Pfeiffer, 2006; Kuiken et al., 1993). These observations suggest that the rarity of adrenal lesions in cetaceans other than beluga and white-sided dolphins is not artifactual.

Several evidences suggest that OC metabolites may cause adrenal cysts. The toxicity of OCs metabolites for the adrenal cortex such as O,p'DDD, noticed during early toxicity assessments of DDT, has long been used for the treatment of pathological adrenal cortex hypersecretion (Cushing syndrome) in both human and veterinary medicine (Hart, Reagan, & Adamson, 1973; Rijnberk, 1996). Other OC metabolites such as $MeSO_2OC$ are adrenocorticolytic in rodents, and some of these compounds, such as 3-$MeSO_2$-4,4'-DDE, compete with GRs and inhibit GC synthesis (Brandt et al., 1992; Durham & Brouwer, 1990; Johansson et al., 1998). In grey and harbor seals from the Baltic Sea, adrenocortical hyperplasia has been attributed to contamination with PCB and DDT based on epidemiological data (Bergman & Olsson, 1985; Olsson, 1994; Olsson, Karlsson, & Ahnland, 1994). In Baltic grey seals, 3-$MeSO_2$-PCB levels were highest in females with adrenocortical hyperplasia (Haraguchi, Athanasiadou, Bergman, Hovander, & Jensen, 1992), a sex distribution reminiscent of that seen in Atlantic white-sided dolphins affected by adrenal cysts.

Both SLE beluga and Atlantic white-sided dolphins are contaminated with high amounts of OCs and their metabolites (Martineau et al., l987; McKenzie, Rogan, Reid, & Wells, 1997; McKinney et al., 2006; Muir et al., 1996; Troisi, Haraguchi, Simmonds, & Mason, 1998). High blubber concentrations of $MeSO_2$-PCB and $MeSO_2$-DDE have been detected in SLE beluga. In fact, these concentrations are the highest among cetaceans, including Hudson Bay beluga (the concentrations found in SLE beluga are also higher than those found in humans exposed to PCB during the Yusho industrial accident) (Letcher et al., 2000 a, b). SLE beluga and white-sided dolphins both form abundant methylsulphones from PCBs. Thus, because of their long life span, both species may have been exposed to high levels of adrenotoxic OC metabolites for decades (Martineau et al., 2003).

There is apparent contradiction between the adrenocortical hyperplasia epidemiologically associated with $MeSO_2$-DDE in seals, and the adrenocortical

degeneration induced by these compounds in laboratory animals and possibly in SLE beluga (Brandt et al., 1992; Jönsson, Lund, Bergman, & Brandt, 1992; Jönsson, Lund, & Brandt, 1993; Jönsson, Rodriguez-Martinez, Lund, Bergman, & Brandt, 1991). Perhaps OC metabolites-mediated degeneration of the adrenal cortex alternates with ACTH-mediated regeneration since in mammals, the destruction of the adrenal cortex and/or the interference with GC synthesis normally triggers the feedback control of the HPA axis. Decreased GC levels due to adrenocortical destruction normally increase the production of ACTH by the pituitary, which leads to hypertrophy (increased cellular size) and hyperplasia (increased cell numbers) of the adrenal cortex in order to reestablish normal serum GC levels. Note that contaminant-induced damage to cortisol-producing cells has been observed in contaminated fish in the St Lawrence River (Hontela et al., 1992; Hontela, 2005; Rijnberk, 1996; Ulrich-Lai et al., 2006). Thus, it is possible that adrenal lesions affect taxonomically divergent species because of environmental exposure to similar adrenotoxic lipophilic compounds.

It is probable that the pathologic effects of ingesting low OCs'doses over decades - such as occurs in free-ranging mammals - differ from those of large single doses typical of toxicity experiments carried out in laboratory animals. SLE beluga, white-sided dolphins, harbour porpoises and Baltic grey seals are exposed to complex and different cocktails of OC compounds which generate different metabolites that alter the distribution and even the nature of each other (van Birgelen, Ross, DeVito, & Birnbaum, 1996). For instance, by contrast to cetaceans, pinnipeds have a high capacity for generating PCB methyl sulphone and have high CYP2B activity (Boon, Oostingh, van der Meer, & Hillebrand, 1994; Reijnders & de Ruiter-Dijkman, 1995; Troisi et al., 1998). The combined pathologic effects of these complex mixtures are probably not the same as those of single compounds or metabolites typically used in toxicological studies. In addition, the effects of toxic xenobiotics vary according to species, sex, genetic background, age and the developmental stage at which experimental animals are first exposed (Jönsson, Rodriguez-Martinez, & Brandt, 1995). For instance, Baltic Grey and Harbor seals contaminated in nature with OC show adrenocortical hyperplasia, a purely proliferative lesion, of which the severity is proportional to tissue OC concentrations whereas in SLE beluga in contrast, a mixture of degenerative and proliferative lesions affects the adrenal cortex (Lair et al., 1997; Olsson et al., 1994). Adrenocortical hyperplasia in harbor porpoises contaminated with OCs is not proportional to their OC tissular levels (Kuiken et al., 1993). This could be related to the relatively higher CYP2B-dependent ethoxyresorufin-*O*-deethylase (EROD) activity or other metabolic differences shared by both harbor porpoises and pinnipeds (reviewed in Martineau et al., 2003).

Conclusion

Noise is a likely source of major stress in marine mammals due to increased anthropogenic activities practiced worldwide in an industrial mode. Stress and some lipophilic contaminants exert their effects through two nuclear receptors, GR and AhR, both present in lymphocytes, and whose functions are

intertwined because they bind common ligands such as NF-κB. For instance, GCs are competed out by some PCB metabolites, and GC synthesis is decreased by AhR activation. In addition, the adrenal glands, the end producers of acute and chronic stress hormones, are themselves the target of some OC metabolites. Thus, it is safe to say that responses to stressors, acute and chronic, are disrupted by at least some OCs and /or DRBPs in contaminated marine mammals. As shown by the seemingly conflicting effects of dioxin exposure on IL-1 production by immune cells from different species, the methods used to assess mechanisms of immunotoxicity *in vitro* have to be standardized in terms of cell types employed (cell line versus primary cells; genetically engineered cells versus non genetically engineered cells; cell mixture versus pure population), duration of exposure (with time course measurements), and contaminants concentration (which should include concentrations found in wild animals) (Neale et al., 2005; Vogel et al., 2004).

Pathologists faced with the task of determining the contributing factors, or the causes of wildlife mortality, rarely have clinical information such as GC circulating or fecal levels. To compensate for this lack, adrenal and pituitary glands of dead or live animals should be examined in details because in animals and people, chronic stress and the accompanying sustained ACTH production over extended periods are expected to lead to macroscopic pathological changes in adrenal glands, of which the most obvious is probably increased mass (Clark, Cowan, & Pfeiffer, 2006; Swaab et al., 2005).

We propose that such baseline data – which could be determined on live animals, by echography or magnetic resonance imaging for instance- would help in assessing the presence of chronic stress when confronted with a declining wildlife population from which it is difficult to extract clinical data (e.g. data from live animals). Concurrently, other means of obtaining GC levels from live animals, such as measuring tissue GCs levels from skin biopsies, should be developed.

To this author's knowledge, there have been no animal toxicity studies to address the effects of stressors on the potential toxicity of environmental contaminants or therapeutic compounds. This is especially true with regards to marine mammals. Yet it is clear from this review that DRPBs can antagonize GC-mediated chronic stress responses: GCs repress the synthesis and release of all proinflammatory cytokines whereas on the contrary, at least in certain cell types, DRPBs increase expression levels of proinflammatory cytokines such as IL-1 β, TNF-α, IL-8, BAFF and of pro-inflammatory transcription factors such as IRF-3. It is also possible that AhR, GR, IRF-3 and NF-κB compete for the same coactivators, and/or that unexpected effects result from cross-talks between these receptors and transcription factors if inflammation, viral infection, DRPB contamination and chronic stress coincide temporally.

Together, the interactions between variable intracellular concentrations of GCs, GR isoforms, mineralocorticoid receptors, cytokines and co-transcription factors such as NF-κB and IRF-3 subtly modulate immune functions during stress, to avoid immune or inflammatory overreactions, or on the contrary to enhance the immune system in order to eliminate microorganisms and/or their toxins (Sapolsky et al., 2000). Any disturbance of this finely tuned system and of its development by xenobiotic compounds through AhR, or by chronic stress through

sustained high GCs levels, is likely to have undesirable consequences on the immune and inflammatory responses. Some of these outcomes might be unexpected. For instance, the inner ear relies on optimal adjustment of GCs, GR and other GR ligands (chaperones, co-chaperones, and modulatory element binding proteins) to avoid damage following audiogenic stressors. The failure to elevate GC levels in response to audiogenic trauma such as those that are likely induced by the intense sound produced by oil exploration might increase damages to the inner ear of cetaceans exposed to such noise (Canlon et al., 2007; Finneran et al., 2002; Horner, 2003).

The exposure to some OCs and to other exogenous stressors such as noise either *in utero* or during early life threatens the integrity of the immature mammalian immune system, and compromise the adaptive response to subsequent stressors. Juvenile cetaceans are often more contaminated than adults because they absorb contaminants from lactating mothers, and some OCs are especially toxic for developing organs such as thymus and brain. Thus juveniles are particularly put at risk by OC contamination and noise.

New or improved conceptual frames for stress have recently emerged (McEwen 1998, 2000; Sapolsky et al., 2000). All confer the HPA axis and its development a central role in the response to stressors. Most consider contaminants as another stressor (Romero, 2004; Sapolsky et al., 2000). Yet at least some of these stressors, DRPBs, target the adrenal glands, the very same organ whose integrity allows mammals to respond adequately to daily stressors.

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