Modulation of Mast Cell and Basophil Functions by Benzene Metabolites

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Abstract: Benzene is a carcinogenic compound used in industrial manufacturing and a common environmental pollutant mostly derived from vehicle emissions and cigarette smoke. Benzene exposure is associated with a variety of clinical conditions ranging from hematologic diseases to chronic lung disorders. Beside its direct toxicity, benzene exerts multiple effects after being converted to reactive metabolites such as hydroquinone and benzoquinone. Mast cells and basophils are primary effector cells involved in the development of respiratory allergies such as rhinitis and bronchial asthma and they play an important role in innate immunity. Benzene and its metabolites can influence mast cell and basophil responses either directly or by interfering with other cells, such as T cells, macrophages and monocytes, which are functionally connected to mast cells and basophils. Hydroquinone and benzoquinone inhibit the release of preformed mediators, leukotriene synthesis and cytokine production in human basophils stimulated by IgE- and non IgE-mediated agonists. Furthermore, these metabolites reduce IgE-mediated degranulation of mast cells and the development of allergic lung inflammation in rats. Both *in vitro* and *in vivo* studies indicate that benzene metabolites alter biochemical and functional activities of other immunocompetent cells and may impair immune responses in the lung. These inhibitory effects of benzene metabolites are primarily mediated by interference with early transduction signals such as PI3 kinase. Together, currently available studies indicate that benzene metabolites interfere by multiple mechanisms with the role of basophils and mast cells in innate immunity and in chronic inflammation in the lung.

Keywords: Mast cells, basophils, benzene, hydroquinone, benzoquinone, histamine, cytokines.

INTRODUCTION

Benzene is a small and relatively stable aromatic hydrocarbon (benzol; 1,3,5 cyclohexatriene; C_6H_6) [1, 2]. It is a widely used industrial chemical and one of the most common air pollutants, the concentrations of which range from 0.1 to 100 parts per billion (ppb) [3, 4]. The role of benzene in causing human health effects has been clearly established particularly regarding to its hematotoxic and carcinogenic properties [5]. Benzene is a chemical intermediate in the production of a wide array of commercial products [6], including drugs, dyes, rubber, plastic paints, linoleum, glue and other adhesives, leather products, enamels and important industrial chemicals [7, 8]. Nonoccupational (environmental) exposure is primarily related to combustion processes, including emissions from vehicles and tobacco smoking (EPA, 2002). The Environmental Protection Agency (EPA) classified benzene as Group A human carcinogen since it induces multisites and multispecies/strains carcinogenic effects in both sexes [9].

STRUCTURE AND METABOLISM OF BENZENE

The chemical structure of benzene comprises six carbon atoms with equidistant C–C bond lengths that are canonically formed with six C–H bonds arranged cyclically [1]. Although benzene is susceptible *in vitro* to aromatic substitution, acylation, sulphonation, nitration, and hydrogenation, *in vivo* it undergoes mainly hepatic oxidation mediated by cytochrome P450 2E1 (CYP2E1) pathways [6, 10, 11] to form open ring and hydroxylated metabolites that are further transformed in the bone marrow [12-14] Fig. (**1**). It is generally agreed that the toxicity of inhaled benzene results from its biotransformation to reactive species [15, 16]. Benzene is metabolized in the liver by CYP2E1 to phenol, which undergoes subsequent hydroxylations to hydroquinone, catechol, and 1,2,4-benzenetriol [4]. Catechol is further oxidized to 1,4-benzoquinone by bone marrow peroxidases or by autoxidation. Similarly, hydroquinone can be oxidized to *p*- benzoquinone either spontaneously [17] or through a peroxidase-mediated pathway [18] Fig. (**1**). As has been shown earlier CYP2E1-dependent metabolism is a prerequisite for the cytotoxic and genotoxic effects of benzene [11]. However, transformation of CYP2E1-generated metabolites within target organs is thought to be a primary mechanism for local generation of toxic molecules [19]. Bone marrow is particularly enriched in oxidative enzymes that are capable of converting benzene and its metabolic intermediates into secondary myelotoxic metabolites [14, 20]. Most evidence suggest that the ultimate toxic species from benzene metabolism are hydroquinone and benzoquinone based, in part, upon comparative toxicity studies in bone marrow cells [21], clastogenicity in human lymphocytes [22] and the capacity to form covalent

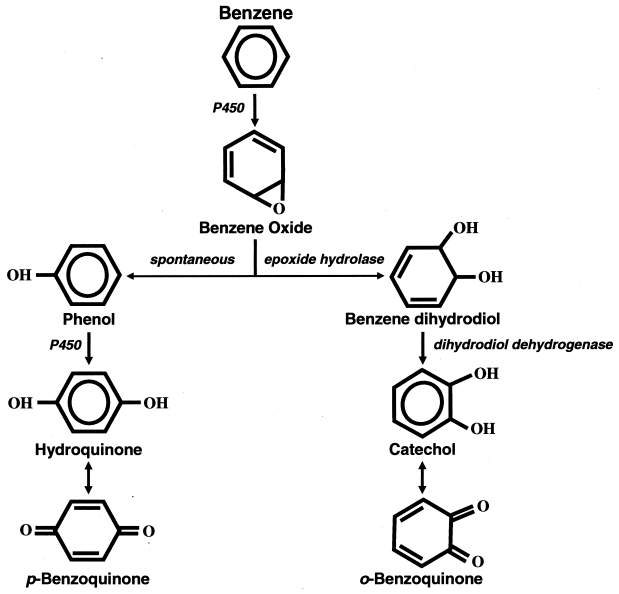

Fig. (1). Metabolic conversion of benzene into reactive toxic metabolites *in vivo*.

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DNA adducts *in vitro* [23]. The intermediate benzene epoxide can also undergo ring opening to trans-muconic acid. Because many reactive metabolites are formed during benzene metabolism, it is likely that benzene toxicity is mediated through multiple pathways. There is increasing evidence that generation of toxic metabolites of benzene is strongly influenced by gene polymorphisms of enzymes involved in its metabolism, particularly CYP2E1 [24-26]. Thus, genetic factors significantly interact with environmental exposure to determine the extent of myelotoxicity and alterations of immune functions induced by benzene.

CLINICAL EFFECTS OF BENZENE EXPOSURE

Exposure to benzene can occur *via* the oral, and/or dermal but the inhalation route is the most important especially in occupational environments [7]. The effects of inhaled benzene on human health depend on the concentration and time of exposure. At 25000 ppm, benzene is lethal within minutes [27]. Limited inhalation of 4000 ppm. can cause giddiness, euphoria, headache and nausea, whereas longer exposures at this level can lead to unconsciousness [27, 28]. Acute (short-term) inhalation exposure of humans to benzene causes systemic toxicity such as narcosis, and at high concentrations, respiratory depression [9, 29]. Chronic (long-term) inhalation exposure has been linked to various hematologic disorders such as aplastic anemia, leukopenia, thrombocytopenia or pancytopenia in occupational setting [9, 30]. There is also evidence in humans which indicates that lung cancer may result from benzene exposure [31, 32]. Reproductive effects have been reported for women exposed to inhalation at high levels and increased incidence of leukaemia has been observed in humans occupationally exposed to benzene [33, 34].

A number of studies indicated that exposure to organic solvents or particle matter containing benzene is associated with lung inflammation. For example, exposure to mixture of organic solvents has been involved in the development of asthma-like symptoms [35-37]. In humans, exposure to particle matter was associated with an increased prevalence of cough and bronchitis [36, 38] and may be responsible for the development of acute and chronic respiratory impairment resulting in chest tightness, dyspnea and rhinitis [39]. In mice, exposure to benzene exacerbates pneumotoxicity [32]. Airborne pollutants, of which benzene is an important constituent, may cause a wide spectrum of immunologically mediated disorders [40, 41] and are recognized as a cause of increased rate of admissions for acute asthma attacks at emergency departments [42]. While these studies confirm that exposure to air pollutants is associated with chronic lung inflammation, they do not establish a clear association between benzene exposure and lung inflammation. On the other hand a number of studies in animal models indicate that benzene and its metabolites may impair lung inflammation by influencing local immune responses. Ribeiro *et al*. showed that exposure to hydroquinone *in vivo* alters circulating neutrophil functions and reduces their migration into the alveolar space in a murine model of LPS-induced lung inflammation [43]. Furthermore, there is increasing evidence that hydroquinone has potent immunosuppressive activities. For example, hydroquinone suppresses the production of inflammatory cytokines, nitric oxide and prostaglandin E_2 in macrophages and leukocytes [44-48]. This benzene metabolite negatively regulates receptor-mediated phagocytosis [44] and the expression of pattern recognition receptors [47]. More recently, the molecular target of the immunosuppressive activities of hydroquinone in macrophages has been identified as the Cys-310 residue of the signaling molecule Akt [47].

Thus, studies on the effects of benzene metabolites on lung inflammation gave different and often conflicting results. It is likely that evaluation of the role of benzene and its metabolites on inflammatory and immune responses in the lung may vary depending on the experimental model used, the way of exposure and the functional responses that are being evaluated.

EFFECTS OF BENZENE METABOLITES ON MAST CELLS AND BASOPHILS

Mast cells and basophils are primary effector cells in allergic disorders including rhinitis, bronchial asthma and anaphylaxis [49]. These cells can be activated by a variety of mechanism that involve cross-linking of surface IgE bound to the their high affinity receptor (FcεRI) or activation of other receptors engaged by bacterial products such as the toll-like receptors (TLR) and formyl peptide receptors (FPR, FPRL1 and 2) [50-52]. Stimulation of mast cells and basophils leads to the release of preformed (e.g. histamine and neutral peptidases) and *de novo* synthesized mediators (e.g. cysteinyl leukotrienes, cytokines and growth factors) [49, 53, 54]. Benzene and its metabolites may influence mast cell and basophil functions either directly or indirectly, through the interaction with other inflammatory and immune cells which in turn regulate mast cell and basophil responses.

Direct Effects of Benzene Metabolites on Mast Cells and Basophils

The effects of benzene and its metabolites on mast cells and basophils have been reported in a limited number of studies. In an early study chronic exposure to benzene was associated with an increase in peripheral blood eosinophil and basophil count [55]. This finding was not consistently reported by other investigators [56]. A primary reason for the discrepancy is that eosinophil and basophil counts were reported as percentage of leukocytes rather than as cells/mm^3. Given the leukopenia frequently associated with benzene exposure, the increase of eosinophils and basophils percentage could be an artifact primarily determined by a reduction of lymphocytes. In spite of these methodological concerns, it appears that basophils are relatively resistant to the myelosuppressive effect of benzene and metabolites as compared to other cells such as lymphocytes and, in some cases, neutrophils.

We have recently investigated the effects of benzene metabolites on human basophils purified from peripheral blood of normal donors. Our results showed that hydroquinone and benzoquinone inhibit mediator release from basophils induced by unrelated stimuli including immunological (anti-IgE), receptor-mediated (f-Met-Leu-Phe) and Ca^{2+}-mobilizing agonists (ionophore A23187). Hydroquinone and benzoquinone significantly reduced histamine release from basophils with the latter being effective at lower concentrations and reaching a more complete inhibition. Hydroquinone completely suppressed cysteinyl leukotriene C_4 (LTC_4) generation stimulated by anti-IgE and f-Met-Leu-Phe as well as IL-4 production induced by anti-IgE [3]. The observation that inhibition of mediator release by hydroquinone and benzoquinone requires a short (5 min) preincubation time and does not occur when the compounds are added after stimulation suggests that hydroquinone and benzoquinone interfere with early transduction signals generated by diverse agonists. Among signals potentially influenced by benzene metabolites a good candidate is the phosphatidylinositol-3-kinase (PI3-K)/Akt pathway Fig. (**2**). This pathway is crucial for degranulation, generation of eicosanoids and production of cytokines in human basophils activated by both IgE- and non IgE-mediated stimuli [57-59]. Natural compounds interfering with PI3-K/Akt pathway, such as luteolin, inhibit mediator release from immunologically activated mast cells [60, 61]. In addition, it has recently been shown that the PI3-K pathway is essential for activation of CCAAT/enhancer-binding protein α (C/EBPα), a key factor for IL-4 production in basophils [62]. The hypothesis that PI3-K/Akt is a primary target of benzene metabolites is supported by the observation that hydroquinone inhibits cytokine production, nitric oxide generation and expression of activation markers in macrophages by preventing PI3-K-dependent Akt phosphorylation [44, 47, 63, 64].

Very little is known on the effects of benzene and its metabolites on mast cells. Repeated exposure of rats to intraperitoneal injection of phenol or hydroquinone does not induce degranulation

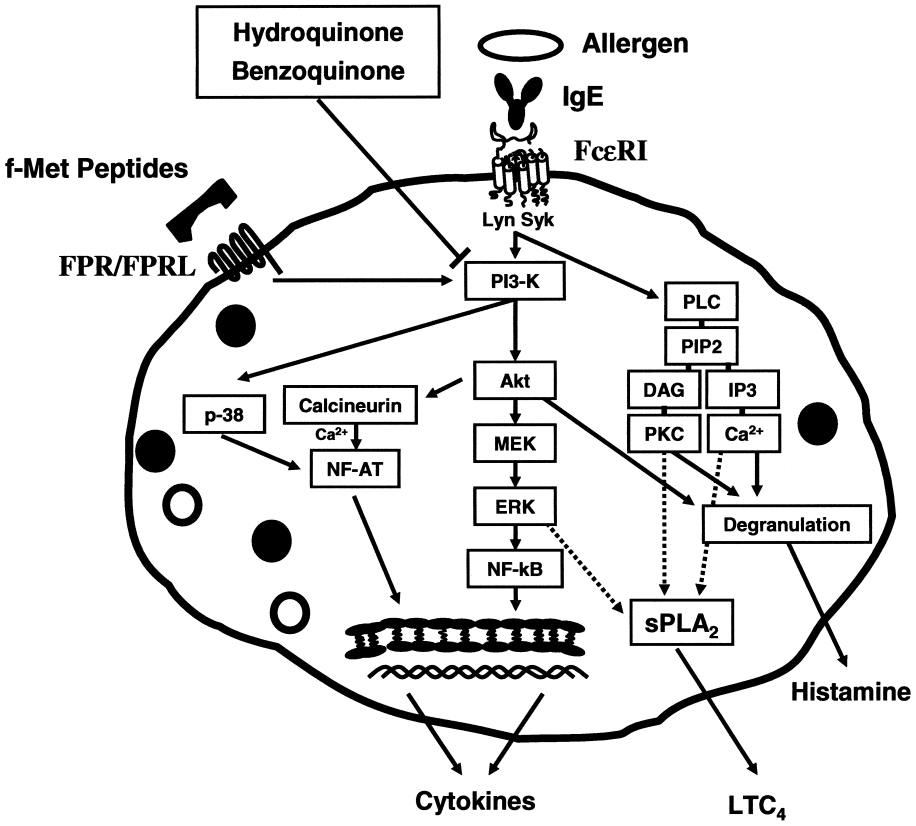

Fig. (2). Proposed mechanism of the inhibitory effects of hydroquinone and benzoquinone in human basophils. Multiple signaling pathways are activated by FcεRI crosslinking and by binding of formyl-containing peptides (f-Met peptides) to FPR and FPR-like receptors. Activation of these pathways results in the release of preformed mediators, generation of cysteinyl leukotrienes, such as LTC_4, and expression and secretion of cytokines, such as IL-4 and IL-13. Hydroquinone and benzoquinone inhibit these responses in human basophils at an early stage presumably by interfering with activation of phosphatidylinositol 3-kinase (PI3-K).

of mesenteric mast cells [65]. Macedo and coworkers examined the effect of hydroquinone in a murine model of allergic lung inflammation *in vivo*. Ovalbumin-sensitized rats exposed to intraperitoneal injection of hydroquinone for 22 days showed a reduction of inflammatory cell number in the bronchoalveolar lavage as well as an impaired contraction of tracheal segments and mast cell degranulation upon allergen challenge [66]. Inhibition by hydroquinone was specific for IgE-mediated mast cell activation since degranulation and mediator secretion induced by compound 48/80 was not influenced. Reduced levels of ovalbumin-specific anaphylactic antibodies (likely IgE and IgG) were found in hydroquinone -treated rats. These effects of hydroquinone were mainly attributed to inhibition of Th2 response and IgE synthesis leading to a lower FcεRI receptor occupancy rather than to a direct effect of this metabolite on mast cells. However, an effect of hydroquinone on intracellular signaling in allergen-stimulated mast cells could not be completely ruled out. At present there are no studies reporting direct effects of benzene and its metabolites on primary human mast cells. Phenylpropanoids containing benzene were shown to inhibit histamine release and TNF-α production from rat basophilic leukemia cells (RBL-2H3) [67]. However, these data cannot be directly extrapolated to benzene and its metabolites.

Together above mentioned data indicate that benzene metabolites exert inhibitory effects on several effector functions of basophils and mast cells. These observations suggest that impairment of cytokine and mediator secretion from these cells may contribute to the global reduction of innate immune responses associated with chronic benzene exposure.

Indirect Effects of Benzene Metabolites Mediated by their Actions on other Inflammatory Cells

Mast cell and basophil functions are modulated by a variety of cytokines and chemokines produced by other inflammatory and immune cells [51]. For example, different T cell subsets can be either positive or negative regulators of human mast cells and basophils. Th2 cells are a primary source of cytokines such as IL-3, IL-4 and IL-13 which drive IgE formation and basophil growth and differentiation. A unique subset of T cells produce IL-9 which supports mast cell growth and survival, enhances FcεRI expression and potentiates cytokine and protease production [68]. IL-10 and TGFβ secreted by regulatory T cells inhibits several functions of human mast cells and basophils including degranulation, eicosanoid synthesis and cytokine production [69]. Other cells of innate immunity, such as macrophages, monocytes and dendritic cells, also interact with mast cells and basophils to orchestrate the first-line defense against bacterial and viral infections and to shape a correct adaptive immune response [70, 71]. Given these tight connections, it is conceivable that benzene and its metabolites may exert indirect effects on mast cells and basophils by interfering with other immunocompetent cells.

The effects of benzene metabolites on the functions of the cells of the immune system can vary and depend on the cell type and the stimulus used to induce the immune response. There is consistent evidence that benzene exposure leads to a decrease in circulating B and T lymphocytes *in vivo* [72-75] and to inhibition of mitogen-stimulated lymphocyte proliferation [76-78]. Hydroquinone inhibits phytohemagglutinin-induced blastogenesis in rat

spleen and bone marrow cells [79] and blocks IL-2 and IFN-γ production in mouse lymphocytes and spleen cells [80]. The latter observations suggested that benzene metabolites, at least in murine models, would act primarily as inhibitors of Th1 responses.

Some studies also suggest that benzene exposure may unbalance T cell-mediated responses toward a Th2 phenotype. For example, benzene metabolites increase secretion of the Th2-type cytokines IL-4 and IL-5 from human peripheral blood mononuclear cells (PBMC) [5] and promote the Th2 type of immune response in LPS-activated macrophages [46, 63]. Intraperitoneal injection of high doses of hydroquinone in antigen-sensitized mice resulted in a significant increase in serum levels of IL-4 and antigen-specific IgE. It should be also mentioned that the production of the potent anti-inflammatory cytokine IL-10 is completely suppressed by hydroquinone and catechol [5]. The enhanced production of Th2 cytokines coupled with the suppression of anti-inflammatory cytokines may further contribute to the development of atopic disorders and may be responsible, at least in part, for the increased prevalence of respiratory allergies in smoke-exposed individuals.

Studies on the effects of benzene metabolites on monocytes and macrophages provided rather conflicting results probably due to the different methodologies and protocols used to reproduce benzene exposure *in vitro*. Some investigators reported an increased production of TNF-α, nitric oxide, and hydrogen peroxide by bone marrow macrophages exposed to benzene [81-83] whereas others have shown inhibition of peritoneal macrophage function by benzene metabolites [64, 84, 85]. Ouyang *et al.* have shown that pretreatment of peripheral blood monocytes with hydroquinone suppresses the production IL-1β, IL-2, IFN-γ and TNF-α without a significant loss of cell viability [86]. In contrast, Gillis *et al.* showed that IL-6 and TNF-α production was enhanced in PBMC treated with catechol and benzoquinone. In parallel experiments, these authors demonstrated that the production of IL-1β and GM-CSF induced by phorbol esters and ionomycin in PBMC was inhibited by benzoquinone and catechol [5].

Taken together these observations indicate that benzene metabolites exert complex and often opposite effects on the production of proinflammatory cytokines depending on the cell examined, the agonist used and the dose and type of benzene metabolites under investigation.

CONCLUDING REMARKS

Benzene and its main metabolites generated *in vivo*, hydroquinone and benzoquinone, strongly influence several components of the human immune system. Experimental studies and epidemiological surveys have clearly shown that exposure to benzene is associated with development of cancer, myelotoxicity and enhanced susceptibility to infections. Occupational exposure to benzene-containing solvents or inhalation of smoke has been associated primarily with development of atopy and asthma-like symptoms. However, *in vitro* and *in vivo* studies clarified some of the mechanisms underlying the development of benzene-associated disorders and suggested that the effects of benzene metabolites may be rather inhibitory on inflammation and immune responses. The inhibitory effects of hydroquinone and benzoquinone on basophils and mast cells suggest that these metabolites are unlikely to be linked to the development of allergic airway inflammation. The suppressive effects of hydroquinone and benzoquinone on basophil and mast cell effector functions may rather reduce the capacity of these cells to participate to innate immune responses. Combined with the inhibitory effects on the other immune cells (T cells, macrophages and monocytes), the reduced functions of basophils and mast cells may participate to a global impairment of innate immunity which may be responsible for the enhanced susceptibility to infections of patients chronically exposed to benzene.

ABBREVIATIONS

CYP2E1	=	Cytochrome P450 2E1
FcεRI	=	High affinity IgE receptor
FPR	=	Formyl peptide receptors
IkBα	=	Inhibitor of NF-κB
IKKβ	=	Inhibitor of nuclear factor κ-B kinase subunit β
LTC_4	=	Cysteinyl leukotriene C_4
PBMC	=	Peripheral blood mononuclear cells
PI3-K	=	Phosphatidylinositol-3-kinase
TLR	=	Toll-like receptors

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