Review Article

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Modulation of mitogen-activated protein kinase by endocrine-disrupting chemicals

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) are used to describe environmental agents that alter endocrine function. They are found in the environment as constituents of consumer products, such as plastic bottles, toys, and pesticides. Mechanisms of action for their effects are not thoroughly understood. Some chemicals may disrupt endocrine function via mitogen-activated protein kinases (MAPKs). Kinases function in signal-transducing pathways involved in regulating key cellular processes in many organisms. These kinases can be activated by various extracellular physiological or pathological stimuli. EDCs initiate stress and induce kinase phosphorylation cascades. This review discusses previous studies regarding MAPK pathways and their role in endocrine disruption. This work highlights the pathological effects of EDCs and describes their impact on MAPK signaling.

Introduction

Endocrine-disrupting chemicals (EDCs) are environmental chemicals that interfere with the endocrine axis. Such chemicals are ubiquitous in human activities (Kim *et al*., 2010). They can be classified into natural and synthetic chemicals, and include estrogen-imitating compounds, such as alkylphenols and alkylphenol ethoxylates, dioxins, and various pesticides and herbicides (Canesi *et al*., 2004b). Examples of EDCs are BPA, DES, MAA, DEHP, and plant constituents as soy-based products that contain the phytoestrogen, genistein (Setchell *et al*., 2001). Bisphenol (BPA) is used in the production of polycarbonate plastics and in many other plastic products, including food can linings, compact disks, and thermal (fax) papers (Canesi *et al*., 2004b). Cadmium (Cd) is released during agricultural and industrial activities (Genchi *et al*., 2020), and is used in electroplating and stabilizing plastics and pigments (Valbonesi *et al*., 2008). Diethylstilbestrol (DES) is a non-steroidal synthetic estrogen that was widely used clinically to prevent abortion in pregnant women (Al Jishi and Sergi, 2017). Methoxyacetic acid (MAA) is the main metabolite of ethylene glycol monomethyl ether, an organic solvent used in the manufacturing of paints, dyes, and fuel additives (Johanson, 2000; Li and Marikawa, 2020). These examples and others display adverse human health effects by altering fetal development (Iguchi, 1998) and causing endocrine dysfunction (Mosconi *et al*., 2002). Additionally, EDCs target reproductive development by acting as regulatory transcription factors (Abdel-Maksoud *et al*., 2019). Definitive mechanisms of action of EDCs on the endocrine system are not thoroughly understood. This lack of clarity has caused increasing concern, especially with intensifying public awareness of EDC health hazards (Henley and Korach, 2006).

EDCs may trigger mitogen-activated protein kinase (MAPK) signaling pathways, such as Erk1/2 and p38 MAPK (Cheng *et al*., 2011; Abdel-Maksoud *et al*., 2018; Qu *et al*., 2018; Yawer *et al*., 2020). MAPKs are a family of serine and threonine protein kinases that help regulate cellular responses to physiological or pathological stimuli (Soares-Silva *et al*., 2016). Numerous environmental chemicals cause stress and induce stress-related phosphorylation cascades (Valbonesi *et al*., 2008). MAPKs cascades act as primary mediators in signal transduction, which is vital for the regulation of gene expression and cellular processes (Guo *et al*., 2020). In mammals, at least 11 members of MAPK exist. Each member is activated by different extracellular stimuli (Teramoto and Gutkind, 2013). The ERK1/2 pathway (p42/44-MAPKs) is activated physiologically by growth factors. Conversely, JNK1/2 and p38MAPK pathways, composed of stress-activated protein kinases (SAPK), are activated by some pathological stressors, such as ultraviolet radiation, heat shock, mutagens, and cytokines (Pollheimer and Knofler, 2005). Environmental chemicals and heavy metals also activate MAPK pathways (Iryo *et al*., 2000; Vahdati Hassani *et al*., 2017).

This work aimed to clarify possible physiological and pathological roles of mitogen-activated protein kinases and to discuss the effects of endocrine-disrupting chemicals on MAPK-mediated stress-related pathways.

Physiology

MAPKs are a group of signal-transducing enzymes specific to eukaryotes (Bigeard and Hirt, 2018). Generally, MAPKs are a family of serine/threonine protein kinases (Gorostizaga *et al*., 2005). These kinases are classified into three transducing pathway cascades: extracellular signal-regulated kinases (ERKs), c-Jun NH2-terminal (JNKs) and stress-activated protein kinases (SAPKs), and p38 MAPKs (Pinsino *et al*., 2015). These MAPK subfamilies require the phosphorylation of both threonine and tyrosine to exhibit maximal activity (Davis, 2000). Stressors evoke phosphorylation of a specific set of MAPKs family members (Meriin *et al*., 1999; Yaglom *et al*., 2003). Active kinases regulate various cellular responses, connections between cell-surface receptors, and important regulatory targets within cells (Chang and Karin, 2001). They control cell survival through transmitting signals from cell surfaces to nuclei in re-

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sponse to chemical and physical stresses (Sun and Nan, 2016). MAPKs are involved in many vital functions, such as cell growth, differentiation, apoptosis, motility, gene expression, mitosis, and survival (Davis, 2000; Pearson *et al*., 2001; Cargnello and Roux, 2011). MAPKs regulate cell survival through stimulation of ERK1/2, which is activated by extracellular stresses (Kyriakis and Avruch, 2001; Kang *et al*., 2003). Conversely, JNK and p38 are linked to the initiation of apoptosis (Xia *et al*., 1995) in response to stress and inflammation.

Different members of the MAPK cascade are involved in monocytic differentiation (Han *et al*., 1993), T cell maturation (Alberola-Ila *et al*., 1995), and mast cell development (Tsai *et al*., 1993). Moreover, ERKs are fundamental in cell cycle initiation by inactivating an MYT cell cycle inhibitory kinase (Palmer *et al*., 1998).

MAPKs cascades function in many processes in male reproductive organs, including differentiation and maturation of germ cells, germ cell apoptosis, blood-testis barrier (BTB) functions, and Sertoli and germ cell connections (Li *et al*., 2009). Sperm capacitation and acrosomal reactions before fertilization and motility acquisition of sperm in the epididymis are also among these processes (Almog and Naor, 2008). The testis is exposed to mild hyperthermia or testosterone suppression in monkeys and rats. p38 MAPK and JNK1 are triggered in germ cell apoptosis (Johnson *et al*., 2008).

Signaling pathway

Other MAPKs with different regulations and functions are also recognized, such as ERK3, ERK5 and ERK7 (Li *et al*., 2009). MAP kinases function within protein kinase cascades. Each cascade consists of three enzymes initiated in the series: a MAPK kinase kinase (MAPKKK), a MAPK kinase (MAPKK) and a MAP kinase (MAPK). In mammalian cells, at least 14 MAPKKKs (Raf-1, A-Raf, B-Raf, Mos, TAK1, MUK, SPRK, MST, MEKK1, MEKK2, MEKK3, MEKK4, Tpl-2, ASK), 7 MAPKKs (MEK1(MKK1), MEK2(MKK2), MEK5, MKK3, MKK4, MKK6, MKK7), and 12 MAPKs (ERK1, ERK2, p38a, p38b, p38g, p38 d, JNK1, JNK2, JNK3, ERK3, ERK4, ERK5) exist (Zhang and Liu, 2002). The activation of MAP3Ks occurs via MAP kinase kinase kinase kinases (MAP4Ks), which interact with small G proteins. MAP4Ks are induced by stress or external stimuli, such as cytokines, growth factors, and exposure of cells to environmental chemicals. Phosphorylated MAP3K will activate MAP2K, and MAP2K will activate MAPK (Li *et al*., 2009). Activated MAPK will subsequently phosphorylate downstream effectors, such as membrane, cytoplasmic and nuclear proteins. The final consequences of these events affect cell cycle differentiation, cell death, cell movement, cytoskeletal status and intracellular trafficking (Boutros *et al*., 2008).

Several factors control signal rate and intensity. These factors include cellular localization of MAPKs and their substrates (Pearson *et al*., 2001), relationships between kinases, and MAPK module and scaffolding proteins (Yoshioka, 2004). Additionally, phosphorylation and ubiquitination are among these factors (Laine and Ronai, 2005).

Pathology

The MAPKs signaling is altered in many diseases. Some stressors, such as mitogens, cytokines, and cellular factors, initiate various MAPK pathways (Fig. 1). Once initiated, phosphorylation and activation of five subcategories of MAPKs follow, involving RSK, MSK, MNK, MK2/3, and MK5 (Cargnello and Roux, 2011). MAPK signaling is also involved in mediating cellular responses to environmental stimuli, such as exposure to EDCs (Kelly and Levin, 2001; Driggers and Segars, 2002; Losel *et al*., 2003). In mammalian cells, estrogen (E2) can initiate rapid actions through non-genomic pathways (Kelly and Levin, 2001; Nadal *et al*., 2001; Driggers and Segars, 2002; Losel *et al*., 2003). These actions can be initiated via different mechanisms, such as local effects through the alteration of ion fluxes, in addition to regulation of gene transcription as a result of activation of cAMP, MAP, PKC and PKA PI-3K kinase cascades (Nadal *et al*., 2001; Driggers and Segars, 2002; Losel *et al*., 2003). Estrogens stimulate cell proliferation and increase intracellular calcium (Saraf *et al*., 2021). Additionally, the rapid estrogen reaction activates membrane receptors for growth factors, such as IGF1R and EGFR, leading to activation of MAPK cascades and AKT signaling (Migliaccio *et al*., 2006; Song *et al*., 2007).

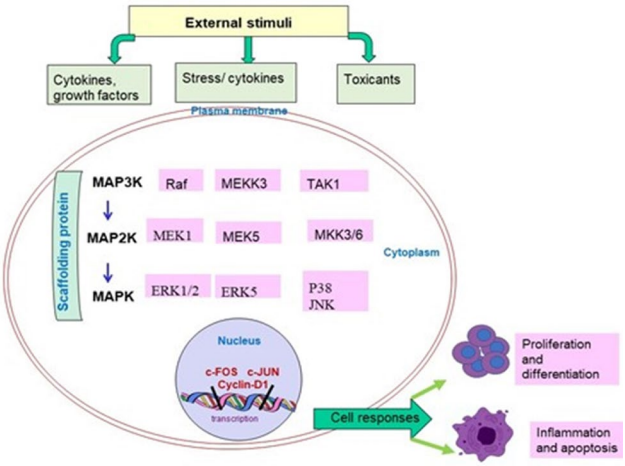

Figure 1. Mitogen-activated protein kinase (MAPK) cascades in mammalian cells.

Activation of MAP kinases in response to non-physiological mediators, such as EDCs, causes a variety of cellular responses. Some EDCs can mimic the rapid reaction of E2 in both calcium and kinase-mediated signaling (Klotz *et al*., 2000; Noguchi *et al*., 2002; Lee *et al*., 2003; Warner *et al*., 2020). The synthetic estrogen, DES, induces constant p38 phosphorylation (Canesi *et al*., 2004a). Also, DES increases phosphorylation of ERK2 MAPK (Canesi *et al*., 2004a). BPA-induced toxicity to colon cancer cells activates MAPK/AKT signaling (Qu *et al*., 2018). BPA rapidly initiates phosphorylation of MAPKs and STATs in hemocytes (Canesi *et al*., 2004b).

Reproductive toxicants greatly affect (MAPK) pathway activity. In turn, cellular responses, such as proliferation, differentiation, and apoptosis are altered (Iseki *et al*., 2005; Wollenhaupt *et al*., 2006; LaChapelle *et al*., 2007; Jin *et al*., 2008; Valbonesi *et al*., 2008). Some environmental toxicants, e.g., cadmium, bisphenol (Wong *et al*., 2004; Wong and Cheng, 2005), and DEHP (Abdel-Maksoud *et al*., 2015; Abdel-Maksoud *et al*., 2018) act on the reproductive system to induce either germ cell depletion from the seminiferous epithelium that supports spermiation, distrurbance of epididymis and testis development, or BTB disruption via one of the three MAPKs, i.e., Erk1/2, p38 MAPK and JNK. For example, after exposure to cadmium, both p38 and ERK MAPKs are activated, leading to reorganization of the BTB and anchoring junction, BTB disruption, and germ cell loss from the epithelium. In contrast, exposure of rats to adjudin causes activation of only ERK MAPK, inducing restructuring of the anchoring junction without perturbing the BTB (Xia *et al*., 2006). This effect can probably be modified with specific inhibitors of p38 or JNK MAPK (Chang and Karin, 2001). Thus, reproductive dysfunction caused by the environmental toxicant can be modulated using substances targeting p38 or JNK MAPKs. Also, exposure of rats to BPA affects male reproductive function; for instance, BPA may disrupt BTB integrity. This effect is mediated through loss of gap junction function and subsequent failure to organize tight junction and anchoring junction functions (Cheng *et al*., 2011). BPA also modified the expressions of tight junction proteins, p38, and JNK MAPK on male fish leading to Sertoli cell junctions (Tao *et al*., 2019). Moreover, ERK activation increases in epididymis from prepubertal male rats exposed to BPA (Abdel-Maksoud *et al*., 2018).

Similarly, ROS produced by many environmental toxicants act as secondary messengers to activate JNK (Gong and Han, 2006; Chandra *et al*., 2007; Ranawat and Bansal, 2008).

Prenatal exposure to genistein or BPA activates Raf1 and Erk1/2 in neonatal testes. Raf1 is a classic mediator of MAPK signaling. Additionally, both Raf1 overexpression and stimulation are frequent in cancers,

where Raf1 is an intermediate in oncogenic responses to various factors (Leicht *et al*., 2007). Raf1 primes cells to the oncogenic effects of exogenous compounds (Pages *et al*., 1999). BPA treatment enhances phosphorylation of JNK, which is implicated in neuronal differentiation and cell stress. BPA also inhibits cell proliferation and viability of neural progenrator cells through modulating MAPK signaling and ROS generation (Kim *et al*., 2010).

In testis, EDCs dysregulate intercellular gap junctions between interstitial cells (Yawer *et al*., 2020). 12-O-tetradecanoylphorbol-13-acetate and lindane are EDCs that disrupt gap junctions between Leydig cells; these actions are mediated by MAPKs signaling. 12-O-tetradecanoylphorbol-13-acetate dysregulates gap junctions via phosphorylation of Ser282 by MAPK-Erk1/2 (Pogoda *et al*., 2016). Likewise, lindane acts via MAPK-p38 through phosphorylation of Ser279/Ser282 (Falk *et al*., 2016).

Phthalates trigger various cancers and greatly exacerbate the development of prostate cancer. These chemicals upregulated p-ERK5 and p-p38 stimulating prostate cell proliferation (Zhu *et al*., 2018). Also, DEHP causes metabolic disorders, including hepatotoxicity in pubertal female mice mediated through Jun-N-terminal kinase (JNK) (Ding *et al*., 2021). Further, p38 MAPK/NF-KB signaling plays a major role in hepatic fibrosis caused by DEHP exposure (Zhao *et al*., 2019).

Phytoestrogens exhibit substantial influence on cellular signaling pathways and significantly alter developmental and physiological events (Guerrero-Bosagna and Skinner, 2014). Their actions target lymphocytes, synovial fibroblasts, and osteoclasts via MAPK/ERK1/2 signaling (Chakraborty *et al*., 2021). Genistein alters extracellular kinases (ERK) and PI-3/AKT pathways and is useful for the treatment of breast cancer (Morito *et al*., 2001). Pathological impacts of EDCs and their underlying mechanisms for mediating MAPK signaling need more exploratory studies.

Conclusion and Future Studies

EDCs may affect human and animal health by causing endocrine dysfunction. Studies on these compounds indicate that EDCs might act via activation of MAPK signaling to alter endocrine system processes. Different and complex mechanisms of action of EDCs combined with their physical and chemical variety require the accumulation of significant additional information. Additional mechanisms for EDCs have yet to be discovered. Thus, further study is necessary to understand the pathogenesis of EDC-induced toxicity and the role of MAP family kinases. Understanding this pathway will help develop a strategy for preventing endocrine disruption.

Conflict of interest

The author decalres that she has no conflict of interest.

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