HHS Public Access

Author manuscript

Neurotoxicology. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Neurotoxicology. 2021 September ; 86: 166–171. doi:10.1016/j.neuro.2021.08.005.

Impact of environmental toxicants on p38- and ERK-MAPK signaling pathways in the central nervous system

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Abstract

There are several candidate signalling pathways that mediate the response of the central nervous system (CNS) cells to environmental toxins. However, much is still to be learned on how these pathways modulate neurotoxicity. The mitogen-activated protein kinases (MAPKs) signalling pathways, which include the extracellular signal-regulated protein kinase (ERK) and the p38-MAPK, are potentially key pathways to regulate CNS responses to environmental toxins. The pathways play leading roles in the transmission of extracellular signals into the cell nucleus, leading to cell differentiation, cell growth, and apoptosis, to name a few. Moreover, exposure to environmental toxins induces p38- and ERK-MAPK activation, which leads to oxidative stress, inflammation, and apoptosis in the CNS. Here, we provide a concise review of the recent evidence demonstrating the role of p38- and ERK-MAPK signaling pathways and their downstream targets in the CNS following exposure to environmental toxicants such as metals, organophosphorus and persistent organic pollutants.

Keywords

MAPK signalling; CNS; metals; organophosphorus; persistent organic pollutants

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Authors' Contributions

Conception - OMI; Manuscript drafting - OMI, JDI; Critical revisions - MA, JB.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of Interest

The authors declare no conflict of interest.

1.0 Introduction

Extracellular stimuli need to be integrated intracellularly for adequate cellular responses. Signal transduction from the external environment is requisite for translating stimuli into intracellular responses that alter gene expression and modulate other cellular activities. Recent research has highlighted the p38- and ERK-MAPK-mediated responses as signaling pathways that mediate cellular responses to diverse environments (Fadda et al., 2020; Kasemsuk et al., 2020; Morganti et al., 2019; Zhu et al., 2019).

Environmental toxins including metals, organophosphorus, persistent organic pollutants, generate signals that are transduced via the p38- and ERK-MAPK pathways into the intracellular compartment where they elicit neurotoxic responses, such as neuronal apoptosis posing a significant risk for neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease (Fu et al., 2017; Phuagkhaopong et al., 2017; Ray et al., 2015; Todd, 2017). Therefore, continuous human exposure to these substances due to increased industrialization elicits major public health concerns. In the following sections, we highlight recent evidence demonstrating the activation of the p38- and ERK-MAPK signaling pathways and their downstream targets in the CNS following exposure to selected metals, organophosphorus and persistent organic pollutants.

2.0 Overview of p38- and ERK- MAPK pathways

2.1 p38- and ERK-MAPK signaling mechanism

Mitogen-activated protein kinase (MAPK) consists of the extracellular signal-regulated kinases (ERKs), p38 mitogen-activated protein kinases (p38), and c-Jun N-terminal kinases (JNKs) subfamilies (Aluko et al., 2021; Kim and Choi, 2015; Krens et al., 2006). MAPK pathways contain three successively activated protein kinases; MAPK, MAPK1, and MAPK2. The MAPK2 is typically activated downstream from cell surface receptors (Morrison, 2012). Each MAPK (p38 or ERK) cascade is initiated by specific extracellular stimuli following the successive activation of MAPK2 and MAPK1 (Figure 1).

The ERK-MAPK pathways are activated by extracellular growth factors via the G-protein coupled receptors (GPCRs), receptor tyrosine kinases (RTK) and cytokine receptors. Following RTK activation, its tyrosine residue is phosphorylated allowing other signaling adapters, such as GRB2 and GAB_1 to bind its phosphotyrosine residue. These adapter proteins, such as GRB2 and GAB_1 is critical for the activation of downstream signaling molecules like RAS. The GTP-bound form of active RAS leads to the activation of its direct downstream effector, RAF, a MAPK2 kinase. The RAF family includes ARAF, BRAF, and RAF1; they phosphorylate and activate the MAPK1 kinase, MEK1/2, which in turn activates ERK1 and ERK2 via phosphorylation. ERK1/2 affect a large number of downstream molecules, such as nuclear components, transcription factors, and membrane proteins – *see review* (Kang and Lee, 2019; Vithayathil et al., 2018).

The p38 pathway consists of p38α, p38β, p38γ, and p38δ, and is activated by stress and mediates immune response, cell survival and differentiation. The p38-MAPK is activated downstream of MAPK2 and MAPK1. The primary MAPK2 are MLK3, MEKK3, MEKK4,

ASKs, TAK1, TAO1 and TAO2, while MAPK1 includes MKK3, MKK4, and MKK6. MAPK2 are activated upstream by mediators, such as TRAF2/TRAF3/TRAF6. Following activation, p38 translocates into the nucleus to modulate factors like CREB and NF-kB amongst others, or remains in the cytoplasm to regulate proteins, such as Bax and cyclin D1 – *see review* (Cuadrado and Nebreda, 2010).

2.2 p38- and ERK-MAPK in the CNS

Neurons and glia respond to their environment to ensure survival, growth, motility, development, amongst other functions. Therefore, each cell must devise a mechanism to effectively respond to external stimuli. One of the such and well-studied mechanisms are the p38- and ERK-MAPK signaling pathways (Morrison, 2012). The p38- and ERK-MAPK pathway participates in a wide array of neurodevelopmental functions, such as those involved in synaptic development (Nakata et al., 2005) neuronal differentiation (Loy et al., 2011; Yoshioka et al., 2015), gliogenesis (Haines et al., 2010), and synaptic pruning (MacInnis and Campenot, 2005), to name a few. They are also involved in several physiologic brains functions, such as learning and memory (Mi et al., 2017), synaptic plasticity, pain mediation (Shao et al., 2020), neuronal excitability (Wittmack et al., 2005), and cognitive functions (del Barco Barrantes et al., 2011).

Alterations to these pathways lead to a variety of CNS and neurodevelopmental disorders, including encephalomyelitis (Birkner et al., 2017), demyelinating disease (Suo et al., 2019), traumatic brain injury (Morganti et al., 2019), Alzheimer's disease (Lim et al., 2019; Munoz and Ammit, 2010), Parkinson's disease (Chen et al., 2018; Ray et al., 2015), Amyotrophic lateral sclerosis (Sama et al., 2017), and Huntington's diseases (Taylor et al., 2013).

Further, several environmental toxins, such as metals, organophosphorus, and persistent organic pollutants induce CNS neurotoxicity via p38- and ERK-MAPK-mediated neuropathology. These neuropathological processes include neuroinflammation (Morganti et al., 2019; Tan et al., 2019), apoptosis (He et al., 2020; Tao et al., 2018), and abnormal neurite formation (Zhou et al., 2019).

3.0 Environmental toxins and CNS p38- & ERK-MAPK signaling

Environmental toxins, such as metals, organophosphorus, and persistent organic pollutants levels have risen due to an increase in industrialization. Contamination of water, air and food by environmental toxicants as a consequence of increasing industrial activities is a major concern for human health. Prolonged exposure to these toxicants leads to their accumulation in the CNS and subsequent neurotoxicities (Fadda et al., 2020; Kasemsuk et al., 2020; Todd, 2017). Their neurotoxic effects are partly mediated via the p38- and ERK-MAPK as reviewed here (Table 1).

3.1 Metals

Metals, particularly heavy metals, are harmful to human health, and prolonged exposure to these metals from sources, such as water, air and food can lead to neurotoxicity – *see review* (Ijomone et al., 2020). Metals readily accumulate in the CNS, where they may elicit "adaptive" neurotoxic responses, such as neuroinflammation and apoptosis (He et al., 2020;

Morganti et al., 2019; Tan et al., 2019; Tao et al., 2018). However, the exact molecular mechanism that mediates these responses are still unclear. Nevertheless, recent works have been aimed at elucidating the role of the p38- and ERK-MAPK signaling pathways in metal-induced neurotoxicity (Kasemsuk et al., 2020; Li et al., 2018; Phuagkhaopong et al., 2017; Zhu et al., 2019).

For instance, manganese (Mn) induced neuronal apoptosis via the activation of the p38-MAPK/CREB pathway downstream of intracellular Ca^{2+} and PKA activation in PC12 cells and mouse brain tissues (Zhu et al., 2019). In human microglia cells, Mn induced oxidative stress and cytotoxicity via the phosphorylation of p38 and ERK signaling proteins. These signaling proteins were activated upstream by LRRK2 kinase activity (Kim et al., 2019). The p38- and ERK-MAPK pathways play a crucial part along with the JNK and Akt pathways in cadmium (Cd) induced cell death of Cd-exposed cerebral cortical astrocytes. Intracellular inhibition of Ca^{2+} by 1,2-Bis(oaminophenoxy) ethane-N,N,N',N'-tetraacetic acid downregulated the p38/ERK-MAPK pathways. This suggests that Cd-Ca^{2+}-p38/ERK-MAPK signaling pathway is involved in Cd-induced cell death in cerebral astrocytes (Jiang et al., 2015). Similarly, (Xu et al., 2016) provided evidence that Cd-induced activation of ERK1/2 and p38 pathways via increased mitochondrial reactive oxygen species in neuronal cells plays a part in neuronal apoptosis. Likewise, apoptotic cell death was observed in Cd exposed mouse brain microvascular endothelial cells. Further studies regarding the underlying mechanism of the Cd-induced cell death showed that the phosphorylated p38- and ERK-MAPK, which was later reversed by selective MAPK inhibitors played an important role (Jung et al., 2008). Methylmercury induced site-specific neuronal degeneration by increasing neuronal loss in the cortex, not hippocampus and cerebellum. This neuronal loss was triggered by the activation of the p38-MAPK/CREB pathway which resulted in downstream c-fos and BDNF upregulation (Fujimura and Usuki, 2017). Mercuric chloride induced DNA fragmentation and cell death prompted an elevation p38- and ERK-MAPK activation leading to increased mRNA expression of Bax and caspase-3 (Fadda et al., 2020).

Further, the p38- and ERK-MAPK signaling pathways are involved in metal-induced neuroinflammation. For example, sub-chronic Mn exposure increased the phosphorylation of thalamic and hippocampal ERK and p38 in rats, which resulted in increased COX-2 protein expression (Li et al., 2018). NF-κB activation downstream of p38-MAPK increased signaling in Mn-induced neurotoxicity in rat mesencephalic cells (MES 23.5), which was significantly attenuated by pretreatment with the p38-MAPK inhibitor, SB239063 (Prabhakaran et al., 2011). In another study, Cd increased IL-6 and IL-8 expression via upstream phosphorylation of ERK1/2 and p38 pathways in human astrocytes (Phuagkhaopong et al., 2017). Likewise, ERK1/2 and p38 were in part involved in Cd-induced production of interleukin IL-6 and IL-8 in human astrocytes. Also, following exposure of U-87 MG cells to $CdCl_2$ at varying doses (1 and 10 μM), there was a dose- and time-dependent up-regulation of CCL2 (C-C motif ligand 2, also known as monocyte chemoattractant protein-1) mRNA expression via an upstream activation of MAPK pathways, including ERK1/2, p38, and JNK, which were selectively inhibited by U0126, SB203580 and SP600125, respectively (Kasemsuk et al., 2020). Mercuric chloride-

induced an inflammatory response evident by an elevation in serum level of TNF-α, IL-6 and brain lipid peroxides via p38- and ERK-MAPK activation (Fadda et al., 2020).

The p38- and ERK-MAPK pathways have also been implicated in metal-induced neurodevelopmental toxicity and CNS disorders. Presenilin, a γ-secretase, is recognized as one of the causes of Alzheimer's disease (Wolfe, 2021). The p38-MAPK/CREB signaling cascades are activated by γ-secretase following Cd exposure and play a role in mediating the induction of COX-2. Thus, this suggests that Cd modulates γ-secretase, resulting in the initiation of p38-MAPK signaling cascades to induce COX-2 expression and apoptosis in C6 astrocytes cells (Lim et al., 2019). Likewise, Cd-induced a dose- and time-dependent up-regulation of CCL2 mRNA expression via an upstream activation of MAPK pathways, including ERK1/2, p38, and JNK (Kasemsuk et al., 2020). CCL2, usually produced by astrocytes, is implicated in cancer metastasis (Lim et al., 2016) and in the neuropathogenesis of Alzheimer's disease (Nordengen et al., 2019). The p38-MAPK pathway has also been implicated in metal-induced developmental neurotoxicity. p38-MAPK signaling was significantly activated in the brain of fish exposed to 100 μg/L Pb during embryogenesis (Lee et al., 2018).

In the foregoing, we have discussed selected metals for which their neurotoxic impact has been associated with modulatory roles on p38- and ERK-MAPK pathways. It is worth stating that since most neurotoxic metals share similar mechanisms of toxicity as well as transporters such as DMT1, transferrin amongst others (Bakulski et al., 2020; Li et al., 2017), it is very likely that other metals besides those discussed here may also impact the CNS p38- and ERK-MAPK pathways. For instance, Mn induces increased AQP4 levels in the plasma membrane of astrocytes surrounding the blood-brain barrier (Rao et al., 2011). Similar findings were seen in iron, lead, and mercury, to mention a few. Increased AQP4 following metal overexposure is implicated in increased water transport, brain swelling, oxidative stress and neuronal death – *see review* (Ximenes-da-Silva, 2016).

3.2 Organophosphates (OPs)

There is evidence that OPs contribute to the etiology of many diseases including neurodegenerative and CNS diseases (Vanova et al., 2018). In addition, oxidative stress and inflammation usually act as the main mechanism in the pathogenesis of these diseases. The OP family includes chlorpyrifos, diazinon, sarin, soman, and trichlorfon, amongst others (Figueroa-Villar et al., 2020). The general exposure routes to OPs are frequently via food ingestion, inhalation, or the skin. Following which they are transported to the nervous system in the plasma and red blood cells bound to acetylcholinesterase (Peter et al., 2014). The MAPK signaling cascades, such as p38 and ERK, are involved in organophosphorus-induced neurodegenerative processes (Lee et al., 2012; Pejchal et al., 2009; Todd, 2017) as reviewed in the following paragraphs.

The most studied organophosphorus is chlorpyrifos (CPF) because of its ubiquitous nature. CPF is a major constituent of insecticide widely used in agriculture, industry, and at home. It has been reported that CPF induces oxidative stress, neuroinflammation, and neuronal cell death (Salyha, 2013) showed that *in vitro* exposure of rat hippocampal cells to CPF resulted in the production of reactive oxygen species, cytotoxicity and eventually, cell death

of hippocampal neurons. Since the MAPK pathways, including the p38 and ERK, have been in the aforementioned neurotoxic events and are activated by CPF, it indicates that CPF has a major role in the induction of apoptosis, inflammation, and oxidative stress via the p38- and ERK-MAPK pathways (Farkhondeh et al., 2020). The investigation on the neurotoxic effects of CPF in PC12 cells indicated that treatment at varying concentrations (0, 25, 50, 100, and 200 μM) induced dose-dependent apoptotic cell death via the increased phosphorylation of the p38- and ERK-MAPK pathways. These MAPK proteins acted as death signals by activating caspase-3 and poly (ADP-ribose) polymerase (PARP) cleavage. These effects were inhibited by specific inhibitors of the MAPK pathways (Lee et al., 2012). Chronic exposure of SH-SY5Y cells to CPF at low concentration increased p38 and ERK phosphorylation, leading to increased cytotoxicity (Todd, 2017). Similarly, CPF treatment of human neuroblastoma SH-SY5Y cells produced cytotoxic effects that appeared to involve an increase in reactive oxygen species. In addition, CPF activated MAPK pathways including ERK1/2, p38, and JNK and resulted in caspase-3 activation. This demonstrates that CPF induced apoptosis by upregulating caspase-3 expression via MAPK activation through reactive oxygen species production and oxidative stress (Ki et al., 2013). Similarly, p38 and ERK was involved in NF-κB nuclear translocation, resulting in increased reactive oxygen species production and oxidative stress. However, the inhibition of p38 but not ERK with rosiglitazone attenuated reactive oxygen species production. Interestingly p-ERK levels were increased by rosiglitazone treatment. Thus, this suggests that rosiglitazone-mediated attenuation of reactive oxygen species generation seemed to be associated with the inhibition of NF-κB, JNK, and p38 signaling pathways, not the ERK pathway (Lee et al., 2014). Further, genomic analysis reveals that sarin activated the apoptotic pathway in exposed rats through the p38- and JNK-MAPK pathways (Te et al., 2015). Exposure of a week old male C57/BL6 mice to 50 or 150 mg/kg of Triphenyl phosphate (TPP) for 30 days resulted in p38-, ERK-, and JNK-MAPK/FoxO-mediated apoptotic cell death in the cortical, thalamic, and hippocampal neuronal population (Liu et al., 2020).

Furthermore, CPF induced increased COX-2 expression in human neuroblastoma SH-SY5Y cells via the upstream activation of p38-MAPK and JNK, but not ERK1/2 (Ki et al., 2013). In rat neonates, subcutaneous CPF (5 mg/kg) exposure in rats from day 11 to day 14 of the postnatal period increased inflammation, which was partly mediated by p38-MAPK/NF-κB inflammatory pathway. This inflammatory change was accompanied by a significant reduction in the number of dopaminergic neurons 16 and 46 days post-exposure to CPF (Zhang et al., 2015). Soman, a known nerve agent, is another highly toxic organophosphate. There is evidence of its activation of the p38-MAPK in cerebellar Purkinje cells *in vivo* to induce its delayed toxicity in the CNS. It increased the expression of phosphorylated p38-MAPK 14 days after poisoning (Pejchal et al., 2009). Prolonged POPs or PFOS exposure in zebrafish during early developmental stages increased MAPK signaling accompanied by several behavioral deficits (Christou et al., 2021). Inferring from the evidence reviewed here, pharmacological targeting and attenuation of the ERK- and p38-MAPK signaling pathways might be an effective new approach to treating OP-induced neurotoxicity.

3.3 Persistent organic pollutants (POPs)

Persistent organic pollutants (POPs) are non-degradable organic compounds. They continually accumulate in the environment, severely affecting human health (Ahmed et al., 2021). Leading to several complications on the nervous system. *In vitro* and *in vivo* studies reveal that POPs cross the blood-brain barrier and impair CNS tissues by exerting oxidative damage (Zhao et al., 2021). In addition, POPs can activate neuroinflammatory pathways by disrupting expressional levels of pro-inflammatory and anti-inflammatory cytokines. Studies evidence that POPs exert their toxic and neurotoxic effects through the p38- and ERK-MAPK signaling cascade. For example, endosulfan, a known POP, increases germ cell apoptosis in *Caenorhabditis elegans*. This apoptotic cell death was regulated by p38-MAPK and JNK cascades. (Wang et al., 2017).

The neurotoxic effect of POPs has also been reported. Perfluorooctane sulfonic acid, for instance, mediated morphologic changes and inflammatory responses in BV2 microglia cells. The corresponding mechanisms involved indicated that PFOS increased TNF-α and IL-6 expression, which were attenuated by JNK and ERK1/2 inhibitor, SP600125 and PD98059 respectively. In addition, there was an increased level of the inflammatory transcription factor NF-κB following perfluorooctane sulfonic acid exposure. These results, taken together, suggested that perfluorooctane sulfonic acid exerts its neurotoxic effects on the response of microglial cell activation via, in part, the c-Jun N-terminal protein kinase, ERK and NF-κB signaling pathways (Zhu et al., 2015). Likewise, tetrachloro-p-benzoquinone markedly induced the phosphorylation of p38, JNK and ERK MAPKs, resulting in a downstream increase in c-jun and c-fos expression and subsequent upregulation of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 (Fu et al., 2017). Also, benzophenone-3 induced apoptotic cell death in neural cells partly via the activation of the p38-MAPK signaling pathway (Wnuk et al., 2018). Other authors have also associated ERK-MAPK signaling pathways and the dopaminergic transmitter system with DEHPinduced morphological alteration in rat striatum and changes in behaviors, such as social interaction and anxiety (Wang et al., 2016).

4.0 Concluding Remarks

The evidence reviewed herein establishes that exposure to environmental toxins, such as metals, organophosphorus and persistent organic pollutants triggers apoptosis, oxidative stress, and neuroinflammation in the CNS through the activation of the ERK- and p38-MAPK signaling pathways. These compounds induce apoptosis and oxidative stress by disrupting the balance of phosphorylation of ERK- and p38-MAPK in animals and *in vitro* models. In particular, p38 and ERK have a modulating effect on numerous downstream molecules, COX-2, caspase-3, IL-6, IL-8, TNF-α and CREB, to mention a few. These downstream molecules modulate inflammation, cell proliferation, differentiation, and apoptosis.

In summary, the impact of environmental toxicants in the initiation and progression of various CNS disorders may be related to their effects on the regulatory roles of key signalling pathways such as the ERK- and p38-MAPK pathways. As such, the pharmacological modulation of the ERK- and p38-MAPK signaling pathways could be

an interesting therapeutic target in combating the impact of neurotoxicity induced by these substances.

Funding

OMI acknowledges the support of the Alexander von Humboldt Georg Forster Research Fellowship for Experienced Researchers (October 2020). MA was supported in part by grants from the National Institute of Environmental Health Sciences (NIEHS) R01ES07331 and R01ES10563. JB acknowledges the German Research Foundation (DFG) funding (BO4103/4-2).

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Highlights

- p38- and ERK-MAPK pathways participates in wide array of neurodevelopmental processes.
- p38- and ERK-MAPK pathways mediate cellular responses to diverse environment.
- Environmental toxicants may trigger CNS disorders via modulation of these pathways

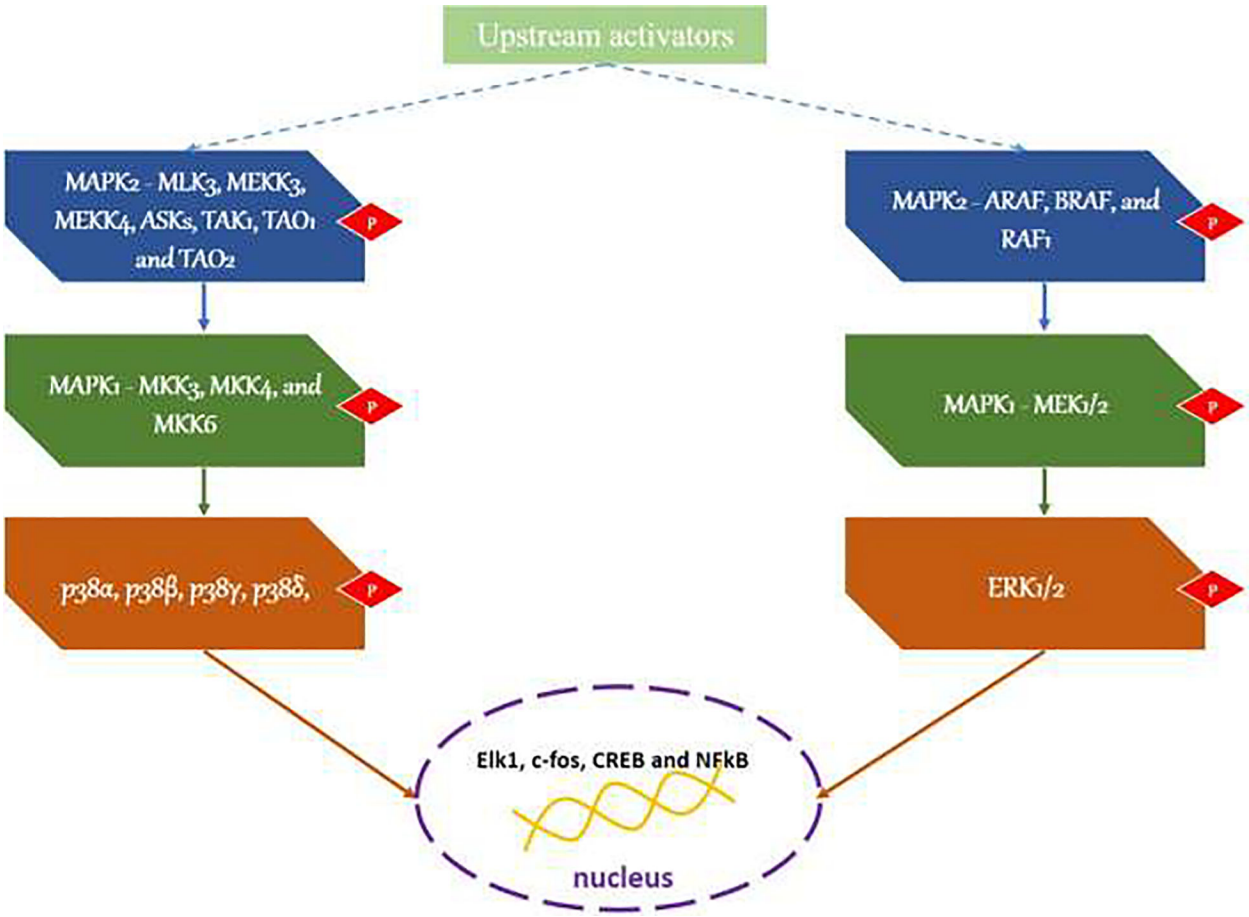

Figure 1:

The p-38 and ERK-MAPK pathways are activated upstream by the phosphorylation of series of specific MAPK2 and MAPK1 modules. Following activation, they translocate into the nucleus or remain in the cytoplasm to modulate the activities of diverse molecular factors; Elk1, c-fos, CREB, and NF-kB. MAPK - mitogen-activated protein kinases; ERK - extracellular-regulated kinase; Elk - ETS Like-1 protein; p - phosphate group, NF-kB - Nuclear Factor kappa-light-chain-enhancer of activated B cells.

Table 1:

Summary of p38- and ERK-MAPK involvement in CNS response to environmental toxicants

Environmental Toxins	Mechanism	Species/Model	Dose	Exposure time/ duration	References
Manganese	Mn-induced neuronal apoptosis via the activation of PKA or Ca^{2+}/p38-MAPK/CREB signaling	PC12 cells and mouse brain tissue	Mice - 20 mg/kg	Mice - Daily intraperitoneal injections for 60 days	(Zhu et al., 2019)
	Mn-induced oxidative stress via increased LRRK2/p38- and ERK-MAPK signaling	Human microglial cells	$MnCl_2$ - 250 μM	24 hours	(Kim et al., 2019)
	Mn-induced inflammation via p38-and ERK-MAPK/ COX-2 signaling pathways	Rat thalamus and hippocampus	$MnCl_2{\cdot}4H_2O$ - 15 mg/kg	12 weeks	(Li et al., 2018)
Cadmium	Cd-induced cell death via that Cd-Ca2+-p38/ERK-MAPK signaling pathway	Cerebral cortical astrocytes	10 μM $CdCl_2$ (chronic exposure) 100 or 300 μM $CdCl_2$ (acute exposure)	12 hours (chronic exposure) 0.5–2 hours (acute exposure)	(Jiang et al., 2015).
	Cd-induced apoptotic cell death via ROS-mediated increase in ERK1/2 and p38 signalling	PC12 and primary neurons from mouse cerebral cortex	10 μM and 20 μM $CdCl_2$	24 hours	(Xu et al., 2016)
	Cd-induced neuroinflammation via increased production of IL-6 and IL-8 ERK1/2 and p38 pathways	U-87 MG cells	10 μM $CdCl_2$	3 hours	(Kasemsuk et al., 2020)
	Neuroinflammation via γ-secretase/p38-MAPK/CREB-mediated increased COX-2 expression	C6 astrocytes cells	10 and 25 μM $CdCl_2$	6 hours	(Lim et al., 2019).
Mercury	Neuronal loss via p38-MAPK/CREB/c-fos/BDNF upregulation.	Mice	30 ppm MeHg	8 weeks	(Fujimura and Usuki, 2017)
	Mercuric chloride-induced DNA fragmentation and cell death via elevated p38- and ERK-MAPK/Bax/caspase-3 signaling	Rat	5 mg/kg $HgCl_2$	14 days	(Fadda et al., 2020)
	Mercuric chloride-induced inflammation evident by an elevation in serum level of TNF-α and IL-6 via p38- and ERK-MAPK activation	Rat	5 mg/kg $HgCl_2$	14 days	(Fadda et al., 2020)
Chlorpyrifos	Apoptotic cell death via increased caspase-3 mediated by p38- and ERK-MAPK signaling pathways	PC12 cells	100 and 200 μM	24 hours	(Lee et al., 2012)

Environmental Toxins	Mechanism	Species/Model	Dose	Exposure time/ duration	References
	Cytotoxicity and neuronal death due to increased p-p38 and p-ERK expression and subsequently increased caspase-3 levels.	SH-SY5Y cells	100 μM	24 hours	(Ki et al., 2013)
	Elevated ROS production via increased p38- and ERK-MAPK/ NF-κB signaling	SH-SY5Y cells	50 – 200 μM	24 hours	(Lee et al., 2014)
Soman	Increased p38-MAPK phosphorylation	Cerebellar Purkinje cells	60 μg/kg	One dose	(Pejchal et al., 2009).
Perfluorooctane sulfonic acid	Increased TNF-α and IL-6 expression partly by increased ERK1/2-MAPK/ NF-κB	BV2 microglial cells	0.1–10 μM	6 or 12 hours	(Zhu et al., 2015)
Tetrachloro-p-benzoquinone	p38, ERK, and JNK mediated increase of TNF-α, IL-1β and IL-6	Rat pheochromocytoma PC12 cells	25 μM	6 hours	(Fu et al., 2017).
Benzophenone-3	p38-MAPK-mediated apoptotic cell death.	mouse neuronal cell (hippocampal and neocortical) culture	25–100 μM	6 or 24 hours	(Wnuk et al., 2018)
Triphenyl phosphate	p38-, ERK-, and JNK-MAPK/FoxO-mediated apoptotic cell death in the cortex, thalamus, and hippocampus.	C57/BL6 mice	50 or 100 mg/kg	30 days	(Liu et al., 2020)