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Commentary

The effects of environmental neurotoxicants on the dopaminergic system: A possible role in drug addiction

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ABSTRACT

Humans are routinely exposed to a vast array of environmental neurotoxicants, including pesticides, endocrine disrupters, and heavy metals. The long-term consequences of exposure have become a major human health concern as research has indicated strong associations between neurotoxicants and a variety of dopamine-related neurological disorders. Developmental exposure to pesticides including paraquat, organochlorines, and rotenone produce alterations in the dopaminergic system and has been linked to neurodegenerative disorders, including Parkinson's disease. Endocrine disrupters such as Bisphenol A, mimic estrogenic activity and impact various dopaminergic processes to enhance mesolimbic dopamine activity resulting in hyperactivity, attention deficits, and a heightened sensitivity to drugs of abuse. A second class of endocrine disrupters, the polychlorinated biphenyls, may act directly on dopaminergic processes to disrupt the dopamine system and produce Parkinson-like symptoms. Exposure to the heavy metal lead enhances dopaminergic activity and has been associated with attention deficits, Alzheimer's disease, and increased drug sensitivity. Manganese exposure, in contrast, results in dopamine deficiencies and Parkinson-like symptoms. Therefore, this commentary will discuss the effects and consequences that exposure to these three classes of environmental neurotoxicants have on the dopamine system and related behaviors and disorders. Finally, the recent hypothesis that exposure to environmental compounds which have effects on dopaminergic neurotransmission, including 2,4-dichlorophenoxyacetic acid, Bisphenol A, and multiple heavy metals, may potentiate drug-induced behaviors and increase the brain's vulnerability to drug addiction will be discussed.

1. Introduction: The dopamine system and environmental neurotoxicants

Dopamine (DA) is a neurotransmitter involved in a variety of central nervous system (CNS) processes, including cognition, motor activity, motivation and reward, mood, attention, and learning. Consequently, any alterations in DA transmission may adversely affect a variety of neurological processes and lead to debilitating behavioral disorders. For instance, Parkinson's disease (PD), a neurodegenerative movement

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Abbreviations: DA, dopamine; DAT, dopamine transporter; VMAT, vesicular monoamine transporter; PD, Parkinson's disease; TH, tyrosine hydroxylase; BPA, Bisphenol A; EDCs, environmental endocrine disrupters; PCBs, polychlorinated biphenyls; MA, methamphetamine.

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disorder, is characterized by the loss of DA neurons and subsequent decrease in DA activity [1]. Conversely, over-stimulation of dopaminergic neurotransmission can lead to hyperactivity and is associated attention deficits, or attention deficit hyperactivity disorder (ADHD) [2]. Dopaminergic neurotransmission occurs through several linked processes, including synthesis, release, uptake, storage, catabolism, and receptor activation (Fig. 1). Tyrosine hydroxylase (TH) converts L-tyrosine to L-DOPA which in turn, is decarboxylated to DA by aromatic L-amino acid decarboxylase. Once synthesized, DA is packaged into synaptic vesicles via transport through the vesicular monoamine transporter (VMAT) and, in response to a presynaptic action potential, is released from the cell. Once released, DA activates a variety of postsynaptic receptors which are coupled to various cell signaling mechanisms. DA transmission is inactivated by reuptake of DA via the DA transporter (DAT) into the presynaptic neuron where it is metabolized by catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). Free, un-metabolized DA is repackaged into vesicles for storage and later use. Due to the heavily regulated and interconnected processes involved in dopaminergic signaling, alterations in a single process may have effects on the other processes involved in DA-associated behaviors. Interestingly, there is a diverse collection of environmental neurotoxicants which selectively target the dopaminergic system, acting on single or multiple aspects of DA neurotransmission to alter behavior (Fig. 1).

Humans are continuously exposed to a variety of environmental neurotoxicants and numerous reports have indicated an association between xenobiotic exposure and human health, including disturbances in the CNS [3]. Although a variety of neurological processes can be adversely affected, the dopaminergic system appears to be a major target for environmental neurotoxicants, including pesticides, environmental endocrine disrupters, and heavy metals. The use of pesticides in agriculture is associated with several

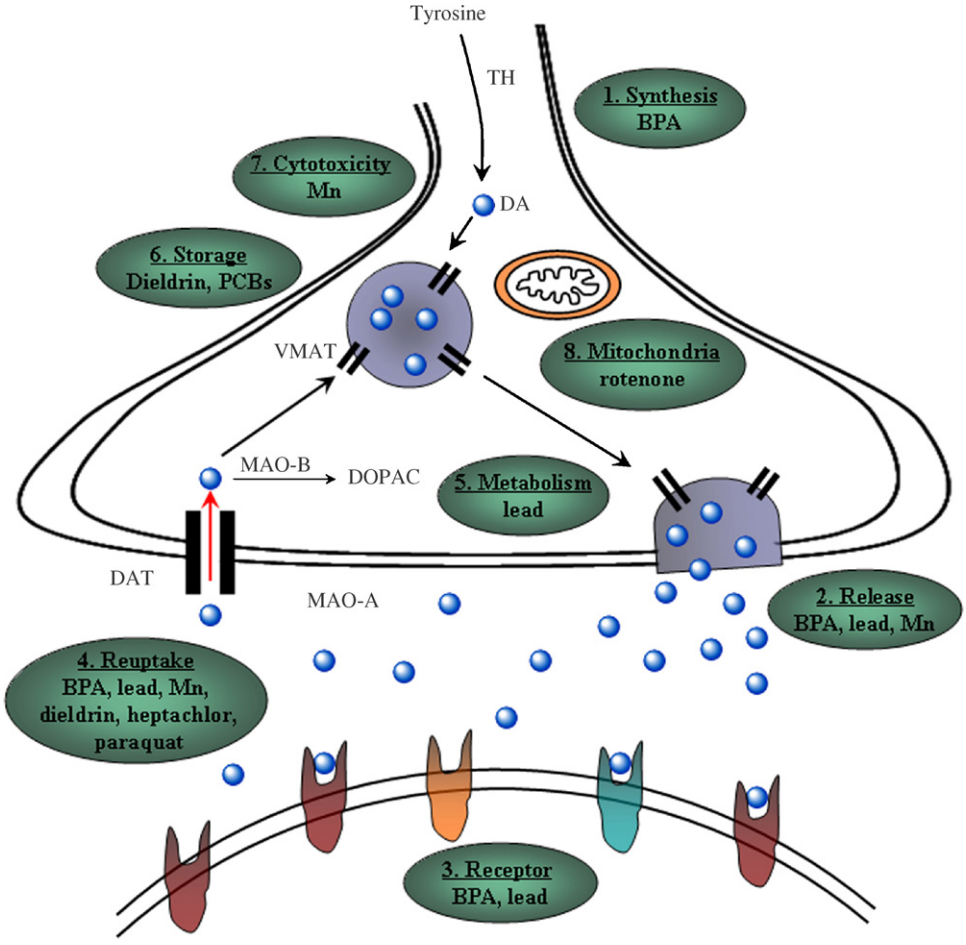

Fig. 1 – Schematic representation of dopaminergic neurotransmission and the effects of various environmental toxicants. Neurotoxicants, including pesticides, endocrine disrupters, and heavy metals can have deleterious effects on multiple processes within the DA system. Endocrine disrupters such as BPA can affect DA synthesis (1) through the regulation of TH expression. BPA and the heavy metals, lead and Mn, have effects on DA release (2) and BPA and lead have effects on DA receptors (3). Inhibition of DAT is a major effect of several chemicals, including BPA, dieldrin, paraquat, heptachlor, lead, and Mn (4). DA metabolism is impacted by lead (5) whereas vesicular storage is affected by dieldrin (6). Mn is cytotoxic to DA neurons (7) and rotenone has effects on mitochondrial respiration (8). By impacting the DA system, environmental neurotoxicants can depress or enhance dopaminergic neurotransmission leading to alterations in DA-associated behaviors and disorders including PD, ADHD, and addiction.

DA-associated disorders of the CNS including PD [4]. Dieldrin, a common organochlorine pesticide, alters DA transmission and has been linked to dopaminergic neurodegeneration and the development of PD [5]. Several other pesticides such as Rotenone [6] and Paraquat [7] have also been linked to the development of PD through alterations in the dopaminergic system. Neuroendocrine disrupters alter endogenous hormonal activity and neuroendocrine functions, including modulation of dopaminergic activity. Bisphenol A (BPA), for instance, has been associated with hyperactivity and an increased sensitivity to drugs of abuse [8], modifies dopaminergic transmission by altering multiple processes, including DA synthesis, DA release and turnover, DAT expression, and the expression of DA receptors [9–11]. Finally, the adverse neurological consequences of human exposure to heavy metals are well documented [12,13]. Developmental lead exposure leads to alterations in multiple aspects of the DA system [14,15] and has been linked to hyperactivity and attention deficit disorders, anti-social behaviors, and senile dementia. Manganese (Mn) is a potent dopaminergic neurotoxicant [16,17] which ultimately leads to impairments in DA-associated behaviors [18]. Therefore, this review will cover the literature describing the effects that environmental neurotoxins have on the dopaminergic system, including DA synthesis and turnover, DAT function, DA receptor signaling, and dopaminergic cytotoxicity. In addition, because the DA system is associated with the reward and reinforcement of drugs of abuse, the recent hypothesis that exposure to certain environmental neurotoxins may influence the development of drug addiction will be discussed.

2. Pesticides

Pesticides are a diverse group of chemicals designed to destroy and repel destructive plants (herbicides), insects (insecticides), rodents (rodenticides), and fungi (fungicides). Rodenticides and fungicides do not appear to have any detrimental or long-term effects on the dopaminergic system. One exception is a manganese-based fungicide, maneb (manganese ethylene bisdithiocarbamate), which has been linked to both the oxidative degeneration of DA neurons and the development of PD-like symptoms [19]. In contrast, there are an overwhelming number of reports implicating herbicides and insecticides as potent dopaminergic neurotoxicants and potential contributors to the etiology and recent increase in the incidence of PD. Therefore, this section will focus on; (1) the herbicide paraquat, which can cause degeneration of DA neurons and PD-like symptoms [19], and (2) a group of insecticides, including organochlorines (dieldrin and heptachlor) and rotenone, which have all be linked to alterations in the DA system and DA-related disorders [19].

2.1. *Paraquat*

Paraquat (1,1′-dimethyl-4,4′-bipyridilium dichloride) is a non-specific commercial herbicide initially synthesized in 1961. The potential contribution of paraquat to dopaminergic neurodegeneration was initially considered following the discovery that MPP^+ exposure resulted in the loss of DA neurons and behavioral symptoms which were remarkably similar to those evident in PD. Paraquat shares a structural similarity to MPP^+, and, when administered to animals, is employed as an experimental animal model of PD [20]. Consequently, it has been suggested that human exposure to paraquat may contribute to the loss of DA neurons and the etiology of PD and epidemiological studies support such an association [21]. That being said, it is important to recognize that the mechanisms of paraquat-induced dopaminergic cytotoxicity are distinct from that induced by MPP^+ as *in-vitro* work indicates that, in contrast to MPP^+, paraquat does not appear to enter the cell through, or inhibit, the DAT [22,23]. On the other hand, a variety of animal studies have reported findings indicating significant deleterious effects of paraquat on the DA system. For instance, administration of paraquat to rats inhibited striatal DA uptake [24] and decreased DAT binding [25]. Oral administration of paraquat to neonatal mice produced reductions in both motor activity and striatal DA levels [26]. Finally, long-term administration of paraquat to rats resulted in the degeneration of mesocortical DA neurons, although there appear to be compensatory mechanisms that help maintain dopaminergic neurotransmission [27]. Taken together, these studies suggest that although paraquat exposure may not reflect the most accurate or consistent animal model of PD, exposure certainly results in oxidative damage to DA neurons and hence, may serve to help us understand the role of oxidative stress in DA neurodegeneration and the etiology of PD [22].

Interestingly, paraquat-induced DA neurotoxicity may be dependent on interactions with other environmental compounds, including maneb [20]. Some investigators argue that humans are rarely exposed to a single pesticide, rather, they are exposed to a combination, and it is this combination that may underlie the contributions of paraquat to the etiology of PD. The combination of paraquat and maneb exposure has been proposed as a potentially more accurate animal model of PD [20]. Cory-Slechta and co-workers have demonstrated a variety of behavioral and physiological effects of the paraquat/maneb combination on the DA system in mice, including decreased locomotor activity (LMA) [28,29], increased oxidative stress [28], reductions in TH and DAT expression, and increased levels of striatal DA [29]. Consistent with these findings are studies demonstrating DA neurodegeneration induced by the paraquat/maneb combination in rats [30]. In conclusion, some groups have been examining the DA degeneration induced by the combination of paraquat and maneb. Indeed, combined exposure to these chemicals is more potent that either chemical alone. It is important to note however, that although a geographic overlap in the use of paraquat and maneb has been identified [31], the potential combinational risk to humans is questionable considering the compounds do not appear to be used in combination [22,32]. Therefore, in investigating the effects of pesticide combinations, which is certainly relevant to human exposure, one must be sure to take into account both the temporal and geographic aspects of the compounds.

2.2. *Organochlorines*

Organochlorines are chlorinated pesticides which were regularly used in agriculture during the mid 20th century.

Although now banned in the United States, due to their high lipophilicity, chemical stability, and lack of degradation, organochlorines persist in our environment. Chronic human exposure to organochlorines occurs at low doses primarily through contaminated food. Of the three major classes of organochlorines; DDT, hexachlorocyclohexanes (lindane), and cyclodienes (dieldrin, heptachlor), a strong correlation between cyclodienes, DA neurotoxicity, and the incidence of PD as been demonstrated in a variety of studies. Therefore, this section will focus on the effects dieldrin and heptachlor on dopaminergic neurotransmission.

Supporting a role of dieldrin in the increased incidence and etiology of PD are reports of increased levels of dieldrin residues in post-mortem brain samples from PD patients [33]. Exposure to dieldrin appears to cause selective dopaminergic neurotoxicity [5,33] through the inhibition of mitochondrial respiration, increased ROS and quinone levels, and the initiation of apoptosis [34]. The end result of the neurotoxic insult induced by dieldrin is manifest as significant depletions in brain DA levels [33]. Although the loss of DA neurons undoubtedly contributes to the decrease in brain DA, other effects of dieldrin on the DA system have been reported, including alterations in transporter levels and activity. For instance, developmental exposure to dieldrin increased the expression of both DAT and VMAT in the mouse striatum [35,36] and increased the susceptibility of DA neurons to MPTP-induced neurotoxicity [5]. In an *in-vitro* cell model, dieldrin inhibited the VMAT [35] yet stimulated the uptake of DA through the DAT [37]. Presumably, increased cellular reuptake of DA coupled to the inhibition of vesicular uptake, would allow for the oxidation of un-sequestered DA to reactive quinones, consequently, increasing oxidative stress and initiating apoptosis.

Heptachlor residues remain environmentally persistent and human exposure usually occurs through the consumption of contaminated food. Recent studies suggest that heptachlor exposure may adversely affect the dopaminergic system, although little evidence linking heptachlor to PD has surfaced. Heptachlor administration to adult C57BL/6 mice increased DAT binding and expression and DA uptake [37,38]. Perhaps counter-intuitively, Miller et al. [38] demonstrated increased VMAT protein levels but inhibited transport activity. In addition to adult exposure, perinatal exposure to heptachlor also increased DAT, VMAT, and TH levels [39]. In summary, the organochlorines dieldrin and heptachlor induce similar deleterious alterations in dopaminergic neurotransmission, yet share little in terms of their potential contributions to the etiology of PD. Understanding the effects of these compounds on the DA system and the contrasting contributions to PD etiology may help in understanding the exact mechanisms underlying the disease.

2.3. *Rotenone*

Rotenone, a naturally occurring insecticide extracted from *Leguminosa* plants, is commonly used for small-scale organic farming. Rotenone exerts its toxic effects through the inhibition of mitochondrial complex I (NADH dehydrogenase), which has been implicated in the pathogenesis of PD [40]. Consequently, it has been suggested that rotenone exposure may contribute to the increased incidence and etiology of PD. Indeed, rotenone-exposed animals show behaviors consistent with PD, including decreased locomotion, flexed posture, and rigidity [6]. However, based on its limited environmental use, short half-life, and limited bioavailability, it is unlikely that rotenone exposure has a significant impact on PD [41]. Consistent with this view is the finding that chronic rotenone inhalation or ingestion fails to confer Parkinsonian symptoms [42]. That being said, rotenone is a potent dopaminergic neurotoxicant, disrupting mitochondrial respiration consequently increasing ROS generation and oxidative stress. In a variety of *in-vitro* and *in-vivo* models, rotenone inhibited complex I of the electron transport chain and increased ROS production [6]. For instance, using three different experimental models of increasing complexity, Sherer et al. [6] reported oxidative damage in a neuroblastoma cell line and midbrain slice cultures exposed to rotenone as well as in the brains of rotenone treated rats. In conclusion, although perhaps not a major player in the pathogenesis of PD, rotenone exposure can have deleterious consequences on mitochondrial respiration and DA cell viability and thus, may provide a unique model for examining the role of the mitochondria in the degeneration of DA neurons and the etiology of PD.

3. Neuroendocrine disrupters

Environmental endocrine disrupters (EDCs) are compounds which target the body's endocrine system consequently altering hormonal activity. Although exposure may also occur through a variety of other mechanisms, humans are typically exposed to EDCs via the consumption of either contaminated food or food that contains natural non-steroidal compounds. Polychlorinated biphenyls (PCBs) are a class of chlorinated organic compounds used, in part, as coolants for transformers and capacitors, additives in PVC coating, pesticide extenders, flame retardants, and hydraulic fluids. Banned in the 1970s, PCBs are still prevalent in the environment and have been linked to a variety of CNS disorders [43]. Although PCBs generally act as endocrine disrupters, they may also directly impact the DA system resulting in Parkinsonian-like symptoms [44]. The impact of PCBs on the DA system appears to be manifest as reductions in extracellular DA [45], likely as a consequence of inhibited DA synthesis [46]. Recent work, however, has also implicated the DAT and VMAT as potential targets. Pharmacological experiments have demonstrated that DA uptake into both synaptosomes [47] and synaptic vesicles [48] is inhibited by PCBs. Consequently, cytosolic DA is not sequestered in synaptic vesicles leading to increased DA metabolism within the cell terminal and the subsequent reduction in extracellular DA levels. Finally, *in-vivo* studies demonstrated that various PCB mixtures have the ability to disrupt DA function via inhibition of DAT and VMAT activity [49]. Therefore, PCBs have demonstrated a direct impact on dopaminergic neurotransmission and while PCB's are certainly not the only environmental compound associated with PD, examining their effects on the DA system may help in understanding the involvement of the DA transporters in the etiology of PD.

The focus of the remainder of this section will be on estrogen and BPA-mediated alterations in the DA system. BPA is an aromatic organic compound which is primarily used in the manufacturing of polycarbonate plastics and epoxy resins and is found in several consumer products including polycarbonate food containers and can liners, dental sealants, compact discs, and PVC piping. An estrogen receptor agonist, BPA acts on the hormonal system to mimic estrogenic activity which includes modulation of dopaminergic neurotransmission. Interestingly, the National Toxicology Program recently issued a report on the potential toxicity of BPA and the Canadian government has acted to label BPA as a toxin and ban its use in plastic manufacturing.

3.1. *Estrogen mediated effects on the DA system*

Prior to discussing any effects that xenoestrogens may have on the DA system, it is important to understand the modulation of DA neurotransmission by endogenous estrogen. Ligand-dependent estrogen receptors (ERs) bind directly to specific estrogen response elements to regulate the transcriptional activity of numerous genes, including genes encoding proteins of the DA system. Consequently, endogenous and exogenous chemicals which bind ERs may indirectly modulate dopaminergic function. For instance, it appears that estrogens impact DA synthesis via the transcriptional regulation of TH [50,51]. Maharjan et al. [50] reported that the effects of estradiol on TH are dependent on the subtype of ER activated as ERα activation increased, and ERβ activation decreased, the transcriptional regulation of TH. Estradiol also manipulates DA neurotransmission through the regulation of DA receptors. Hruska and Nowak [52] demonstrated increased sensitivity and an up-regulation of DA D1 receptors in the rat striatum following estradiol treatment. Interestingly, estradiol exposure resulted in a down-regulation of DA D2 receptor mRNA, although the protein levels were unchanged suggesting that decreased mRNA was likely a secondary effect of enhanced DA release [53]. Finally, estrogen-implanted female rats displayed both positive and negative changes in DA receptor expression depending on brain region [51]. These rats also demonstrated an increased sensitivity to cocaine leading the authors to suggest that estrogenic regulation of the DA system may impact the behavioral response to cocaine [51]. In summary, it is well documented that endogenous estrogens are involved in the regulation of the dopaminergic system via a variety of mechanisms and it is possible that environmental estrogens may have indirect, estrogen-mediated, effects on the DA system.

3.2. *Effects of BPA on the dopamine system*

BPA (4,4′-isopronylidenediphenal) was one of the first non-steroidal synthetic estrogens and due to its strong cross-linking properties the chemical industry uses it to produce polycarbonates. BPA activates both of the major types of ERs (ERα and ERβ) in the anterior pituitary to modify estrogenic activity. Consequently, BPA may regulate the transcriptional activity of genes targeted by the estrogen system, including dopaminergic genes. The consequences of BPA exposure on the DA system have only recently begun to be elucidated and a variety of behavioral modifications in animals have been reported, including hyperactivity and impulsivity [9], two key symptoms of disorders such as attention deficient hyperactivity disorder [54].

BPA-induced alterations in the DA system can be presynaptic, affecting DA synthesis, DAT expression, and DA release and turnover [9,10]. Ishido et al. [9] reported that neonatal exposure to BPA significantly decreased TH immunoreactivity in the rat SNpc suggesting decreased DA synthesis. The decrease in TH expression was independent of the route of administration as both acute intracisternal injections and chronic oral administration to rat pups resulted in comparable changes in TH expression [9]. TH activity and DA synthesis are upstream events in dopaminergic neurotransmission and thus, once TH expression is perturbed, processes downstream, including DA release and DAT activity, could also be affected. Indeed, perinatal BPA exposure alters the release and turnover of DA [10]. Pregnant rats were orally administered varying doses of BPA during gestation and the postnatal period and neurotransmitter levels were then measured in both the female rat pups and the Dams. At 3 weeks old, levels of DA metabolites in the brains of pups perinatally exposed to BPA were significantly elevated and the ratio of metabolite/DA increased in a dose-dependent manner [10]. The authors also found increased metabolite/DA ratios in the occipital and frontal cortex of the Dams [10], indicating that perinatal exposure to BPA increases DA turnover in both the treated Dams and their female offspring. In addition to its effects on DA release, both experimenter-induced acute injections and chronic oral administration of BPA lead to a significant decrease in DAT mRNA levels in the midbrain of 8-week-old pups [9]. Moreover, using cDNA microarray technology, the same group reported finding decreased gene expression profiling for DAT [55] supporting the finding of BPA-induced reductions in DAT mRNA.

In addition to presynaptic changes, effects of BPA on dopaminergic activity may be postsynaptic by altering the expression of DA receptors [8,56]. Microarray analysis has demonstrated down-regulation of DA D4 receptors in the rat midbrain following neonatal exposure to BPA [11,55]. The DA D3 receptor has also been implicated as receptor binding studies in mice treated neonatally with BPA showed a reduction in functional D3 receptors in the limbic region, although D3 synthesis and mRNA expression remained unchanged [56]. Interestingly, BPA induced the up-regulation of DA D1 receptor mRNAs, which are involved in cocaine-associated behaviors [57], in mice following prenatal and neonatal exposure [8]. Finally, G-protein activation experiments showed that BPA treated mice had increased DA-induced G-protein activation, an effect which was attenuated with a DA D1 antagonist indicating a D1 dependent mechanism [8].

In conclusion, evidence indicates that BPA exposure leads to alterations in the DA system, including effects on DA synthesis, release, uptake, and receptor activation. As an environmental estrogen, it is the predominant thought that the estrogen receptor-mediated transcriptional regulation of TH expression is the principal event and any effects on the downstream processes are consequences of decreased DA synthesis. In contrast, it is also plausible that BPA may act on

the dopaminergic system directly and independent of estrogen receptors [58]. Further research is needed to elucidate the mechanisms involved in both estrogen-mediated and estrogen-independent mechanisms involved in BPA-altered dopaminergic neurotransmission. Due to the variety of effects that BPA has on the DA system, it is easy to speculate that BPA, and other environmental estrogens, may affect behaviors mediated by dopaminergic activity, including the brain's reward/reinforcement processes.

4. Heavy metals

Heavy metals are naturally occurring elements with high atomic weights such as lead, manganese (Mn), and cadmium. Humans are routinely exposed to heavy metals through a variety of sources. Lead, for example, can be found in old paint (lead was banned from paint in 1978), leaded gasoline, computers and televisions, vinyl blinds, and drinking water. On the other hand, exposure to manganese is often occupational as it is used as an alloy to harden steel and aluminum, and a component in the manufacturing of ferroalloys, dry cell batteries, and fungicides. Heavy metals can accumulate in human tissue and induce severe toxicity; consequently, exposure to these metals is a major health concern. Heavy metal exposure is associated with a variety of DA-related behavioral abnormalities including anti-social behaviors, attention deficits, Alzheimer's disease (AD), and PD.

4.1. *Effects of lead on the dopamine system*

Lead, which does not have any known physiological function, penetrates the BBB and interferes with the normal functioning of the CNS resulting in a variety of behavioral impairments. Lead neurotoxicity is manifest as alterations in dopaminergic neurotransmission [14,15]. For instance, chronic exposure to lead evoked accumbal DA release in post-weaned rats while the synaptic clearance of DA was reduced, suggesting that the DAT may be a target for lead [15] and indicating that lead-induced alterations in the CNS can occur in both adolescence and adulthood. However, because the developing brain, including the dopaminergic system, is continuously undergoing changes, it is highly sensitive to the effects of lead resulting in overactive or supersensitive DA neurotransmission. Thus, although lead exposure does have effects on adults, the effect of lead on prenatal and childhood development has been a major health concern for decades. Multiple groups have reported on the effects that prenatal or neonatal exposure to lead has on the developing DA system [12,14]. Rats exposed to lead *in-utero* and through lactation displayed lower DA levels and increased rates of DA turnover in the cortex and striatum [12,14]. Interestingly, gender appears to play a critical role as female offspring were significantly more sensitive than males [12]. Finally, neonatal exposure via a lactating Dam significantly decreased MAO levels, hence, inhibiting DA metabolism [59]. It is interesting to note that a low dose of lead increased, whereas a large dose decreased, DA levels suggesting that dose has a major impact on the effects of lead on DA neurotransmission.

An enhanced DA D1/D2 receptor sensitivity in rats exposed prenatally to lead has also been described as quinpirole-induced locomotor behavior was enhanced in the offspring of lead-exposed Dams [14]. Unfortunately, the relationship between lead and DA receptors appears to be more complex than a straightforward enhancement of receptor sensitivity. Using drug discrimination procedures, Cory-Slechta and Widzowski [60] demonstrated a super-sensitivity of D1 and D2 receptors in rats postnatally exposed to lead. D1 receptor super-sensitivity remained persistent in the presence of a D2 antagonist leading the authors to suggest that the discriminating behaviors for DA agonists were not a result of D1/D2 interactions [61]. Lead exposed rats also had decreased levels of MK-801 binding, an effect which was reversed by the DA agonist, apomorphine, but not the selective D1 agonist SKF-82958, implicating a D2 dependent mechanism and suggesting that lead exposure could lead to disturbances in glutamate/DA interactions [61]. Finally, the initial super-sensitivity of DA receptors appears to be transient as the discontinuation of drug discrimination results in a sub-sensitivity of both D1 and D2 receptors [62]. In summary, there is convincing evidence indicating adverse effects of lead on the DA system, however, it appears the effects are dependent on a variety of factors, including dose, gender, and developmental stage of exposure. Interestingly, due to its effect on the mesolimbic DA system, a variety of recent studies have reported on the enhanced sensitivity of lead-exposed animals to cocaine and other rewarding drugs of abuse [60,63].

4.2. *Effects of manganese on the dopamine system*

Human exposure to large amounts of Mn is often occupational in nature, although exposure to humans also occurs through the ingestion of food. Mn^{2+} functions as a cofactor for a number of enzymatic reactions and is thus, an essential trace nutrient for all forms of life. However, excessive accumulation of Mn in the brain can have long-term toxic consequences on the DA system and associated behaviors [16]. Mn accumulates in the basal ganglia where it exerts a cytotoxic effect on DA-containing neurons. The cytotoxic impact of Mn accumulation is characterized by the neurodegeneration of DA neurons [16,17] and decreased extracellular DA [64]. Behaviorally, rats exposed to Mn had decreased spontaneous motor behavior and conditioned avoidance responses [18]. Non-human primates also show PD-like motor deficiencies accompanied by a pronounced decrease in DA release when exposed to Mn [64]. Recent evidence implicates cellular oxidative stress [65] and alterations in DAT function [16] as mechanisms underlying Mn-induced neurotoxicity. Mn-induced inhibition of mitochondrial respiration [66] permits the donation of electrons directly to oxygen resulting in reactive free radicals, which subsequently participate in the oxidation of cellular proteins. A second mechanism of Mn-induced ROS generation, via the oxidation of DA, has also been demonstrated in CATH.a cells [17]. In support, Diaz-Veliz et al. [18] demonstrated that the behavioral effects of Mn, decreased spontaneous motor behavior and conditioned avoidance, are potentiated by inhibiting DT-diaphorase, an enzyme responsible for reducing quinone species.

Whether it is employed as a transport mechanism for Mn or serves as a target for Mn-induced ROS, the DAT appears to play

an important role in Mn-induced dopaminergic neurotoxicity. A variety of studies have demonstrated that Mn is taken up into dopaminergic cells through the DAT. GBR12909, a specific DAT inhibitor, decreased the accumulation of Mn in both striatal synaptosomes and the globus pallidus of rats fed a diet high in Mn [67]. In addition to serving as a transport mechanism for Mn, DAT proteins are also molecular targets for Mn-induced ROS, resulting in decreased levels of DAT activity and binding [68–70]. Supporting the non-human primate data, imaging studies in humans occupationally exposed to Mn also showed reductions in specific DAT binding [70]. In contrast to chronic administration, acute Mn exposure appears to cause a transient increase in DAT levels in living non-human primates [69]. Chen et al. conducted a set of *in-vitro* experiments and demonstrated that, in disagreement with their *in-vivo* results, Mn decreased the number of DAT binding sites and inhibited DA uptake [69]. These findings lead the authors to suggest that the increase in DAT levels observed *in vivo* may be a compensatory response to Mn-induced DAT inhibition and that the transient increase in DAT levels may reflect an early event in Mn neurotoxicity which predisposes the DA cell to oxidative damage. In conclusion, Mn intoxication adversely affects dopaminergic neurotransmission, consequently disrupting DA-associated processes including the sensitivity and response to drugs of abuse [71].

5. Potential contribution of environmental dopaminergic neurotoxins on addiction

Addiction is a broad term encompassing the many interactions between sociological, behavioral, and biochemical aspects of compulsive behaviors such as gambling, sex and drug use. Drug addiction is an ongoing human health concern as indicated by recent epidemiological data from the office of Substance Abuse and Mental Health Statistics of the U.S. Department of Health and Human Services (http://www.oas.samhsa.gov/nsduh/2k6nsduh/2k6Results.pdf). Drug addiction is characterized as a compulsive pattern of drug-seeking and drug-using behaviors that continues despite adverse consequences. Physiologically, addiction may refer to a complex condition consisting of multiple adaptations in the brain leading to dependence, withdrawal, tolerance, and sensitization [72]. During the transition from recreational use, in which the drug is taken to achieve a pleasurable experience, to addiction, where the drug is often taken to alleviate craving and distress, an enduring drug-induced neural plasticity alters brain function and the response to drugs [73]. Many people try illicit drugs, however, only a fraction develop physiological dependence hinting that addiction is a likely result of both genetic and environmental influences and that users who develop a dependence on a particular drug likely have an underlying vulnerability to addiction. Although one source of this vulnerability may be genetic in nature, the environment may also play an important role in the development of addiction. Recently, several investigators have begun examining the potential influence that exposure to environmental neurotoxicants may have on the physiological changes associated with addiction. The rewarding and reinforcing effects of drugs of abuse are largely mediated by the DA system and there are reports on the effects of environmental dopaminergic neurotoxicants, including 2,4-dichlorophenoxyacetic acid (2,4-D), BPA, and heavy metals, on drug addiction.

5.1. *Dopaminergic mechanisms underlying drug addiction*

Several anatomically independent brain regions, including the amygdala, hypothalamus, hippocampus, and frontal cortex, are affected by drugs of abuse. Each of these regions participates differently, yet function together to influence responses to rewarding stimuli and the development of addiction. Although addiction is undoubtedly the consequence of alterations in the complex circuitry among multiple brain regions, a major player in mediating drug reward and the development of addiction is the mesolimbic DA system [73]. This pathway, consisting of dopaminergic connections between the ventral tegmental area (VTA) and the nucleus accumbens (NAc) of the limbic forebrain, controls the detection and response to novel, motivationally relevant cues and is activated by rewarding stimuli, including psychostimulants and other drugs of abuse. For instance, cocaine targets accumbal DAT proteins, inhibiting DA reuptake and consequently flooding the brain with DA [74] to produce hyperactivity, restlessness, and a feeling of euphoria. Long-term consequences of chronic cocaine abuse and DAT inhibition are manifest as alterations in DA neurotransmission. A variety of studies analyzing post mortem brain tissue from human cocaine abusers have demonstrated several alterations in dopaminergic proteins, including the DAT [75,76] and DA D3 receptor [77]. DAT binding studies in human brain tissue have demonstrated increased DAT binding in the brains of cocaine users [75]. Furthermore, in agreement with the data indicating increased DAT binding sites is the finding of increased DAT function (DA uptake) [76]. However, paradoxically, cocaine appears to decrease DAT mRNA expression [75]. A second dopaminergic protein that appears to be increased in cocaine abusers is the DA D3 receptor [77] which has been associated with behavioral sensitization and drug dependence [78]. The effect of cocaine on D3 levels is most likely a compensatory response to the increase in extracellular DA produced by the inhibition of DAT.

Another commonly abused drug that targets the DA system to enhance DA neurotransmission is methamphetamine (MA). MA is a potent CNS stimulant causing users to experience an increase in focus and mental alertness, the elimination of fatigue, and a sense of euphoria. The major dopaminergic target of MA is the DAT as it essentially reverses the flow of DA through the transporter therefore increasing extracellular DA [74]. As a consequence of chronic over-stimulation of the DA system, the MA user develops alterations in multiple dopaminergic processes, including changes in DAT and VMAT activity, reductions in DA content, DAT density, and TH activity [79]. Post-mortem examination has indicated reductions in DA and TH levels as well as DAT binding in MA users [80]. Moreover, positron emission (PET) studies, in addition to identifying reductions in DAT, also demonstrated a marked decrease in both VMAT and DA D2 receptor levels [81,82]. Interestingly, reductions in DAT levels persisted once the MA user had remained abstinent for an extended period of time [82] suggesting that MA-induced changes in the DA system

may be permanent. On the other hand, since these differences in dopaminergic proteins persist after drug use has been interrupted, rather than being drug-induced, perhaps these differences existed prior to drug use and it is these irregularities which predispose a person to addiction. For instance, genetic or environmental influences may have altered the DA system in such a way that the brain's vulnerability to cocaine, MA, or other drugs of abuse was enhanced.

5.2. *Effects of pesticides on drug-induced behaviors*

Although a variety of pesticides including paraquat, dieldrin, and heptachlor target the DA system and have been implicated in the etiology of neurodegenerative diseases, there is little evidence linking pesticide-induced dopaminergic alterations to the development of drug addiction. One exception however, is the systemic herbicide, 2,4-D, which has been shown to increase an animal's sensitivity to amphetamine [83]. Animals exposed to 2,4-D during gestation and development up to post-natal day 90 (PND90) displayed increased DA-associated behaviors such as rearing and rotation, an effect which was exaggerated when the animals were challenged with amphetamine [84]. Using [^{3}H]nemonapride binding assays, the authors also demonstrated increased DA D2 receptor levels in multiple brain regions of 2,4-D treated rats [85]. The extent of the changes was both gender and brain region specific as females appeared to be more sensitive than males while the largest effect was found in the striatum. Interestingly, a second group of animals which was treated with 2,4-D from gestation day 16 through weaning, or PND23, showed no behavioral or physiological effect of 2,4-D treatment [84] on PND90, suggesting that the interruption of herbicide treatment may reverse the effect. However, when challenged with amphetamine, the DA-associated behaviors and increase in D2 receptor levels become apparent leading the authors to speculate that perhaps this exposure regime (gestation through PND23) may cause long-term alterations in the functional state of the DA system which may be elicited by amphetamine [83].

5.3. *Effects of BPA on drug-induced behaviors*

The DA-associated behavioral and rewarding effects of cocaine and amphetamine appear to be, in part, modulated by estrogenic activity [86,87]. For instance, estradiol implanted rats demonstrated an increased sensitivity to cocaine suggesting that estrogenic regulation of the DA system may impact the behavioral response to cocaine [51]. As discussed in Section 3, exposure to the xenoestrogen, BPA, results in alterations in multiple dopaminergic processes, ultimately leading to enhanced DA neurotransmission, hence, similar to estradiol, BPA may also mediate some of the dopaminergic effects produced by psychostimulants and other drugs of abuse. Indeed, recent evidence suggests that BPA-induced changes in the DA system may increase the sensitivity to drug-associated behaviors [8,88,89]. Fetal and neonatal mice were exposed to various concentrations of BPA via their mothers during gestation and lactation. At 7 weeks old, the male pups were challenged with either MA or morphine and LMA and conditioned place presence studies were conducted (Fig. 2). Prenatal and neonatal exposure to BPA enhanced MA [8] and morphine [88,89] induced behaviors in a dose-dependent manner (Fig. 2), suggesting that BPA-treated animals had enhanced DA systems and a heightened vulnerability to the rewarding effects of these drugs. Although the mechanisms underlying the effect of BPA on drug-induced behaviors is unknown, rtPCR analysis demonstrated that BPA caused an up-regulation of DA D1 receptor mRNA [8]. Moreover, the D1 antagonist, SCH23390, attenuated the effects of MA in BPA treated pups suggesting a D1-dependent mechanism [8]. Interestingly, the up-regulation of DA D1 receptors appears to coincide with a down-regulation of functional D3 receptors [56]. This group of investigators also demonstrated that BPA has an effect on DA-induced stimulation of G-proteins. By measuring [^{35}S]GTPγS binding in the limbic forebrain of the mouse pups exposed to BPA, the authors demonstrated that BPA increased DA induced G-protein activation suggesting that these effects are mediated via a G-protein coupled receptor [8,88]. SCH23390 attenuated the effect of BPA on G-protein activation again indicating a D1 dependent mechanism. In contrast to its effects on MA and morphine-induced behaviors, BPA treatment resulted in reductions of amphetamine-induced behaviors [90]. Reasons for this discrepancy are unknown and more research is needed to further elucidate any role that BPA may have in the development of drug addiction. Nevertheless, taken together, these results indicate that exposure to environmental estrogens during development can impact adult behaviors and sensitivity to the rewarding effects of drugs of abuse.

5.4. *Effects of heavy metals on drug-induced behaviors*

Lead-induced changes in the DA system including increased DA turnover and receptor super-sensitivity tend to enhance overall DA neurotransmission, therefore, it has recently been suggested that developmental lead exposure may increase the brain's vulnerability to drug addiction. Adult animals who were exposed via their mothers to lead during gestation and lactation periods had increased sensitivity and self-administered cocaine at higher rates then non-exposed controls [63]. This finding is consistent with the evidence demonstrating that lead stimulates behaviors associated with chronic cocaine administration, such as drug seeking and taking [91] suggesting that it may play a role in the development of addiction. These findings indicate that developmental lead exposure can cause long-lasting changes in the responses to drugs of abuse.

Although exposure typically depresses, rather than enhances, dopaminergic function, Mn has also been shown to have effects on psychostimulant vulnerability. Interestingly, animals exposed to high doses of Mn demonstrated opposite responses when challenged with different doses of cocaine [68]. When treated with a lower dose of cocaine, Mn exposed animals displayed increased LMA whereas, when challenged with a high dose of cocaine, LMA was reduced suggesting that chronic exposure to Mn may increase the sensitivity of DA receptors. Consequently, a low dose of cocaine should increase LMA while a high dose may cause stereotyped behaviors yet decrease locomotion [68]. Amphetamine-induced behaviors are also impacted by Mn exposure

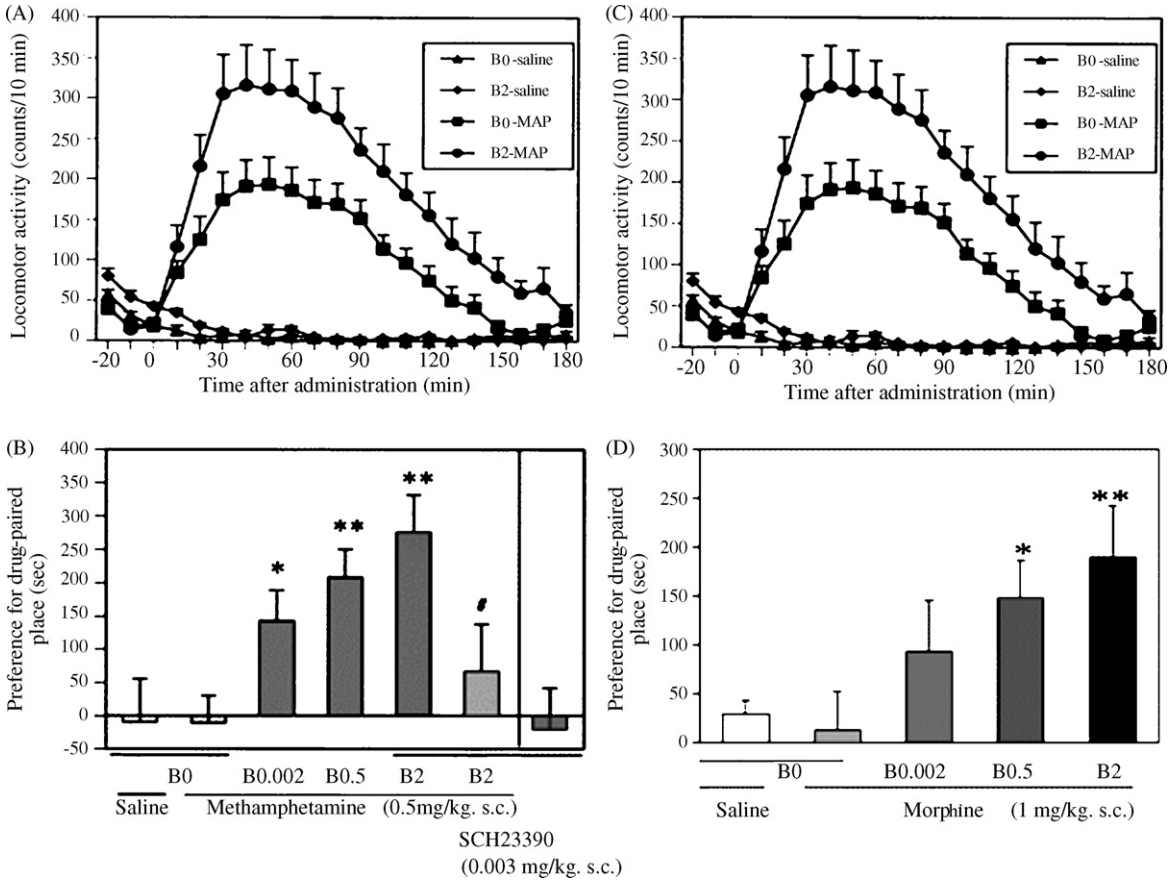

Fig. 2 – Effects of developmental BPA exposure on methamphetamine and morphine-induced behaviors in 7-week-old male mouse pups. Pregnant animals were divided into four groups and exposed to various concentrations of BPA (B0; 0.0 mg/g, B0.002; 0.002 mg/g, B0.5; 0.5 mg/g, and B2; 2.0 mg/g of food) through food consumption. Offspring were exposed to BPA through their mothers. Prenatal and neonatal exposure to BPA increased MA (A) and morphine (C) induced LMA suggesting a heightened sensitivity to the drugs in a dose-dependent manner. Conditioned place preference in response to MA (B) and morphine (D) was also increased in BPA treated animals in a dose-dependent manner. Interestingly, the effect of BPA on MA-induced conditioned pace preference is attenuated with the DA D1 receptor antagonist SCH23390 indicating a D1-dependent effect (B). Adapted from [8] and [89] with permission.

as Mn leads to increases in the behavioral response to amphetamine in young adult rats [71]. Although these findings suggest that Mn exposure alters the responsiveness to psychostimulants, there is clearly a lot of work to be done in elucidating the contributions (if any) of Mn on the susceptibility to addiction.

A third heavy metal that has recently been examined for a potential impact on drug-induced behaviors is cadmium. Interesting, unlike lead and Mn, rather than increasing the sensitivity to drug-induced behaviors, developmental exposure to cadmium results in an attenuated response to cocaine as cocaine self-administration, cocaine-induced behavioral sensitization, and cocaine/saline discrimination were all reduced in cadmium treated rats [92–94]. In addition to blunting the effects of cocaine, chronic cadmium exposure also attenuated MA-induced hyperactivity [95] and the development of morphine sensitization [96]. Although the mechanisms underlying cadmium-induced attenuation of drug-associated behaviors are unclear, it appears that cadmium exposure results in reduced DA turnover in several brain regions [97]. Additionally, dietary cadmium attenuates amphetamine-evoked DA release from striatal slices [95], supporting the hypothesis that cadmium's effects on drug-induced behaviors is mediated, in part, through decreases in brain DA levels. In summary, the literature suggests that exposure to three heavy metals, lead, Mn, and cadmium, may contribute to the behavioral responses elicited by drugs of abuse. While lead and Mn appear to increase an animal's sensitivity to rewarding drugs, cadmium attenuates the behavioral response. Therefore, understanding the diverse mechanisms underlying the effects of these heavy metals on the development of addiction could contribute to a better understanding of the molecular mechanisms underlying drug dependence and addiction.

5.5. *Effects of toxicants on DA-induced cell signaling mechanisms associated with addiction*

DA receptors are coupled to G-proteins which activate multiple cell signaling mechanisms. Consequently, any disturbances in DA receptor levels may have an impact on

downstream cell signaling proteins. One major signaling mechanism coupled to DA receptors is the cyclic adenosine monophosphate (cAMP) pathway, which activates (phosphorylates) cAMP binding protein (CREB), a transcription factor involved in the regulation of a several genes. It is well established that cocaine and other drugs of abuse up-regulate cAMP signaling in the NAc and the development of drug addiction appears to be mediated, in part, via CREB-induced transcription [72]. Interestingly, a number of environmental neurotoxicants which target the DA system also have effects on cAMP signaling and CREB activation. For example, the organochlorine, methoxychlor increased phosphorylated CREB when applied to isolated rat brain mitochondria [98]. Chlopyrifos, an organophosphate which generally targets the cholinergic system but has indirect effects on DA neurons, significantly elevated phosphorylated CREB in rat primary neuronal cultures [99]. Finally, using isolated pancreatic islet cells Quesada et al. demonstrated that exposure to low levels of BPA stimulates the phosphorylation of CREB [100]. In summary, these findings provide some *in-vitro* evidence suggesting that environmental compounds may have effects on DA receptor coupled cell signaling mechanisms (CAMP/CREB) associated with addiction.

6. Conclusions

A large variety of studies have demonstrated that a vast assortment of environmental neurotoxicants have deleterious effects on the dopaminergic system, consequently enhancing or impairing DA neurotransmission and disrupting DA-associated behaviors including motor control, motivation and attention, and potentially, vulnerability to drug addiction. Pesticides and insecticides, such as dieldrin, paraquat, and rotenone, tend to decrease DA activity and can lead to diseases such as PD, which are characterized by dopaminergic neurodegeneration. Heavy metals, including lead, manganese, and cadmium have differential effects on dopaminergic activity, however, all three metals have been shown to disrupt the behavioral response to drugs of abuse and may contribute to the addiction process. Endocrine disrupters, such as BPA, have deleterious effects on the DA system by increasing overall dopaminergic activity and have been linked to hyperactivity and attention deficits. BPA increases an animal's response to drug-induced behaviors and thus may influence the development of addiction. Although reports associating neurotoxicant exposure and dopaminergic disorders such as PD and ADHD are abundant in the literature, studies examining any potential effects of neurotoxicants on drug addiction are just recently being conducted and published. To date, taken together, these studies appear to demonstrate a link between environmental neurotoxicant exposure and drug addiction although much work needs to be done to further identify and characterize the underlying mechanisms involved.

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