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Adeno-associated virus vector-mediated expression of DJ-1 attenuates learning and memory deficits in 2, 2′, 4, 4′-tetrabromodiphenyl ether (BDE-47)-treated mice

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HIGHLIGHTS

- BDE-47 induces ROS-caspase-3-dependent activation of PKCδ.
- BDE-47 stimulates NF-κB nuclear translocation and proinflammatory cytokine release.
- BDE-47-induced hippocampal inflammation leads to learning and memory deficits.
- AAV vector-mediated DJ-1 expression reverses BDE-47-induced neurotoxicity.

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ABSTRACT

Evidence indicates that oxidative stress is the central pathological feature of 2, 2′, 4, 4′-tetrabromodiphenyl ether (BDE-47)-induced neurotoxicity. Protein kinase C delta (PKCδ), an oxidative stress-sensitive kinase, can be proteolytically cleaved to yield a catalytically active fragment (PKCδ-CF) that is involved in various neurodegenerative disorders. Here, we showed that BDE-47 treatment increased ROS, malondialdehyde, and protein carbonyl levels in the mouse hippocampus. In turn, excessive ROS induced caspase-3-dependent PKCδ activation and stimulated NF-κB p65 nuclear translocation, resulting in inflammation in the mouse hippocampus. These changes caused learning and memory deficits in BDE-47-treated mice. Treatment with Z-DEVD-fmk, a caspase-3 inhibitor, or N-acetyl-L-cysteine, an antioxidant, blocked PKCδ activation and subsequently inhibited inflammation, thereby improving learning and memory deficits in BDE-47-treated mice. Our data further showed that activation of ROS-PKCδ signaling was associated with DJ-1 downregulation, which exerted neuroprotective effects against oxidative stress induced by different neurotoxic agents. Adeno-associated viral vector-mediated DJ-1 overexpression in the hippocampus effectively inhibited excessive ROS production, suppressed caspase-3-dependent PKCδ cleavage, blunted inflammation and ultimately reversed learning and memory deficits in BDE-47-treated mice. Taken together, our results demonstrate that DJ-1 plays a pivotal role in BDE-47-induced neurotoxic effects and learning and memory deficits.

1. Introduction

The family of polybrominated diphenyl ethers (PBDEs) has been used as flame retardants in various materials, such as electric appliances, textiles, furnishings, and building materials [1]. PBDEs are not fixed by chemical combination in the polymer product

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and can migrate into the environment and bio-accumulate in the food chain [2]. Humans can be exposed to PBDEs via diet, inhalation, and dermal absorption of house dust [3,4]. Indeed, PBDEs have been detected in human blood, adipose tissue, and breast milk [5,6], as well as in the postmortem brain [7]. Because of their long half-lives and bioaccumulation in the environment and human tissue [8,9], concerns have been raised about the potential toxicity of PBDEs, primarily on thyroid disruption, developmental neurotoxicity, and behavioral neurotoxicity [10–12,5]. 2, 2′, 4, 4′-tetrabromodiphenyl ether (BDE-47), one of the most predominant congeners (accounts for 50%), has been reported to cause learning and memory deficits after prenatal or neonatal exposure [13–17]. Epidemiological evidence further indicates that early-life exposure to BDE-47 might influence children neurodevelopment and cause cognitive dysfunction in children [18–20]. Though the mechanisms underlying BDE-47 neurotoxicity remain unclear, accumulating evidence suggests that oxidative stress plays a key role [21–23].

Our previous work demonstrated that caspase-3, a key cell death effector protease, plays an important role in oxidative stress-induced hippocampal injury [24,25]. Evidence has shown that caspase-3 may be activated by BDE-47 exposure in SH-SY5Y cells and mouse brain [26–28,22]. Protein kinase C delta (PKCδ), an important member of the novel PKC isoform, is an oxidative stress-sensitive kinase that acts as a critical downstream mediator of reactive oxygen species (ROS) [29,30]. Evidence has shown that PKCδ is a substrate for active caspase-3 and it is generally believed that PKCδ is proteolytically cleaved to generate a constitutively activated catalytic fragment (PKCδ-CF) which is known to induce inflammation via activation of NF-κB [31,32]. Chronic brain inflammation has been shown to impair learning and memory in mice following neurotoxin exposure [33,34]. Therefore, we inferred that PKCδ-CF might play a crucial role in BDE-47-induced neurotoxicity.

DJ-1, a product of *PARK7*, is a multifunctional protein that performs functions in oxidative stress and transcriptional regulation. It has been especially investigated as a neuroprotective protein linked to recessively inherited Parkinson's disease [35]. Current evidence also suggests that the cytoprotective roles of DJ-1 are involved in other neurological disease including stroke, amyotrophic lateral sclerosis, and Alzheimer's disease [36–38]. Our preliminary data showed that BDE-47 reduced DJ-1 expression in mouse hippocampi, implying a possible role of DJ-1 in BDE-47-induced oxidative stress.

We postulate that upon oxidative stress, PKCδ is activated by caspase-3-mediated cleavage and subsequently induces PKCδ-CF-dependent inflammation, resulting in learning and memory deficits in mice. It was further speculated that the activation of hippocampal ROS-caspase-3-PKCδ signaling and learning and memory deficits in BDE-47-treated mice could be linked to change of DJ-1 expression. Benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethyl ketone (Z-DEVD-fmk) is special caspase-3 inhibitor [31]. N-acetyl-L-cysteine (NAC), a thiol-containing compound, is an antioxidant that has been shown to have neuroprotective effects [39,40]. In this study, we employed them to confirm that BDE-47 treatment induces PKCδ activation and neuroinflammation via ROS-caspase-3 signaling. Adeno-associated viral (AAV) vectors have emerged as an efficient and safe gene therapeutic tool, and have been used in brain to treat neurological diseases [41]. We thus employed AAV-DJ-1 to express DJ-1 in the hippocampus of BDE-47 treated-mice and investigated whether DJ-1 prevented BDE-47-induced hippocampal inflammation by attenuating oxidative stress. This study was designed to address these issues.

2. Materials and methods

2.1. Animals and treatment

2.1.1. Animals

Seven-week-old male C57BL/6J mice were obtained from Beijing Vital River (Beijing, China). All experimental protocols and

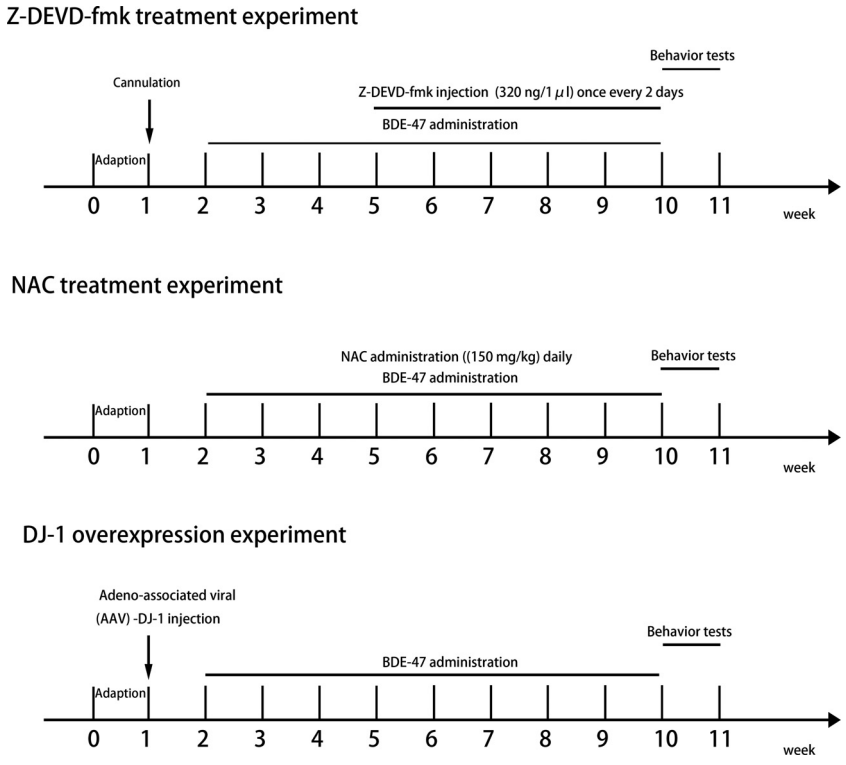

Fig. 1. Timeline of experimental procedures. Mice arrived from supplier at 7-week-age.