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Chronic Low Level Exposure to Organophosphates

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Abstract

Purpose: The purpose of the work reviewed in this abstract was to evaluate potential treatment strategies against the negative effects of the highly toxic class of chemicals, the organophosphates (OPs), on a fundamental process in neurons, axonal transport (AXT).

Methodology: Using a time-lapse imaging technique, we evaluated OP effects on fast AXT of fluorescent membrane-bound organelles in cultured primary cortical neurons from rats. We also developed a manganese-enhanced magnetic resonance imaging (MEMRI) method for real-time measurements of AXT rates in mice in the olfactory system over a single scanning session. Both methods were used to evaluate therapeutic strategies designed to enhance AXT rates.

Findings: Our previous neuronal culture and animal experiments indicated that exposures to OPs of different classes (e.g., insecticide and nerve agent) can lead to impairments of AXT, a potential mechanism of the long-term neurological impairments observed in humans exposed to OPs. Subsequent in vitro phenotypic screening studies indicated that some currently prescribed drugs (lithium chloride, methylene blue) with multi-target pharmacological activity could have potential as repurposed drugs for OP-related neurological impairments as a result of their ability to attenuate the deleterious effects of OPs on AXT. We have also developed an MEMRI method where real-time measurements of AXT rates can be determined in living mice in the olfactory system over a single scanning session. Using this method, we determined that AXT rates were slower in aged vs young mice. In aged mice, the microtubule stabilizing compound Epothilone D was associated with significant improvements in AXT rates. The conclusion of these studies was that our new MEMRI method is sensitive to the negative effects of aging on AXT as well as microtubule-focused therapeutic strategies for improving AXT. Future studies will focus on OP effects/therapeutic strategies using this method.

Research Limitations: All of the studies described in this report were conducted in vitro or in animal models.

Practical Implications: Our studies further suggest that impairments of AXT may underlie the long term deleterious neurologic effects that have been associated with OPs. Moreover, we have identified compounds that could potentially be used to attenuate the negative effects of OPs on AXT.

Value and Originality: The value of the methodology we have developed for assessing the effects OPs on AXT lies in its potential for elucidating novel therapeutic targets and treatment strategies against OP toxicity. The results could have therapeutic implications for conditions that have been associated with repeated OP exposures, such as Gulf War Illness and Aerotoxic Syndrome.

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Keywords

pesticide, nerve agent, Gulf War illness, aerotoxic syndrome, axonal transport, therapeutic strategies

1 Introduction

The chemicals known as the organophosphates (OPs) are found in hundreds of products used worldwide including pesticides, defoliants, fire retardants, industrial solvents, lubricants, plasticizers, and fuel additives (Soltaninejad and Shadnia, 2014; Costa 2018). Many OPs can be highly toxic and associated with acute symptoms (also known as the cholinergic crisis) which include excessive secretions, cardiorespiratory depression, and seizures, which can be life threatening (reviewed, Pereira et al., 2014). These acute symptoms can also lead to a variety of long-term neurological and psychiatric consequences in survivors. In contrast to acute OP poisoning, the long-term consequences of repeated exposures to levels of OPs below the threshold for acute "cholinergic" toxicity are less clear and controversial, but long-term neurological and psychiatric consequences have also been associated with this type of exposure as well as chronic conditions such as Gulf War Illness and Aerotoxic Syndrome (reviewed Naughton and Terry, 2018). While there are antidotal regimens available to treat the symptoms of acute OP toxicity, there are no established treatments for the long-term neurological consequences of OP exposure. It is now well recognized that OPs, in addition to inhibiting the cholinergic acetylcholinesterase (AChE), can negatively affect multiple protein targets as well as biological processes. Studies in our laboratory over the past 20 years using both in vitro and in vivo models indicate that relatively low level exposures to some OPs can lead to impairments in axonal transport (AXT). Given the fundamental nature of AXT to neuronal health, we rationalized that this process might serve as a general focus area for novel therapeutic strategies against OP toxicity. In the first series of published studies reviewed in this Abstract (see Naughton et al., 2020), we employed a multi-target, phenotypic screening, and drug repurposing strategy for the evaluations of potential novel OP-treatments using a primary neuronal culture model and time-lapse live imaging microscopy. In the second series of (unpublished) studies reviewed in this Abstract, we developed a manganese-enhanced magnetic resonance imaging (MEMRI) method where real-time measurements of AXT rates can be determined in living mice in the olfactory system over a single scanning session. Using this method, we evaluated the effects of aging on that AXT rates in mice and subsequently evaluated a potential therapeutic strategy designed to enhance AXT rates.

2 Methods

2.1 In Vitro Studies

Using a time-lapse live cell imaging technique, we evaluated OP effects on fast AXT of membrane bound organelles (MBOs) in rat primary cortical neurons that contained the amyloid precursor protein (APP) tagged with the fluorescent marker GFP. Subsequently, two multi-target compounds, lithium chloride (LiCl) and methylene blue (MB), which are FDA-approved for other indications (Bipolar Disorder and methhemeglobinemia, respectively), were evaluated for their ability to prevent the negative effects of the OP, diisopropylfluorophosphate (DFP) on axonal transport.

2.2 In Vivo Studies

A noninvasive MEMRI method was developed for measuring AXT in living mice in real time in olfactory receptor neurons, which project from the olfactory epithelium to the olfactory neuronal layer (ONL) of the olfactory bulb. Using this new MEMRI method, two major experiments were conducted: 1) an evaluation of the effects of age on AXT in wild-type mice and 2) an evaluation of the effects of microtubule stabilizing compound Epothilone D on axonal transport in aged, wild-type mice.

3 Results

3.1 In Vitro Studies

In these studies, we replicated previous work where the OP, DFP was found to impair AXT in a concentration-dependent manner. The results also indicated that both LiCl and MB prevented DFP-induced impairments in anterograde and retrograde AXT velocities in a concentration dependent manner.

3.2 In Vivo Studies

In these studies, we improved upon previous MEMRI approaches to develop a method where real-time measurements (32 time points) of AXT rates in mice can be determined over a single scanning period. The new MEMRI method is sensitive to the negative effects of aging on AXT in wild type mice. The brain-penetrant, microtubule stabilizing compound Epothilone D administered once per week for eight weeks was associated with significantly increased rates of AXT in aged mice.

4 Summary and Conclusions

Our previous animal and neuronal culture experiments indicated that exposures to OPs of different classes (e.g., insecticide & nerve agent) can lead to impairments of AXT, a potential mechanism of the long-term neurological impairments observed in humans exposed to OPs. Our recently published in vitro phenotypic screening studies indicated that some currently prescribed drugs (LiCl, MB) with multi-target pharmacological activity could have potential as repurposed drugs for OP-related neurological impairments as a result of their ability to attenuate the deleterious effects of OPs on AXT. While in vivo studies will be required to confirm our in vitro findings, these experiments support the potential of LiCl and MB as repurposed drugs for the treatment of the long-term neurological deficits associated with OP exposure (currently an unmet medical need). In more recent (unpublished) experiments we developed an improved (noninvasive) MEMRI method where real-time measurements of AXT rates can be determined in vivo (mice) in the olfactory system over a single scanning session. Using this method, we determined that AXT rates were clearly slower in aged vs young mice. In aged mice, the brain-penetrant microtubule stabilizing compound Epothilone D was associated with statistically significant improvements in AXT rates. The conclusion of these studies was that our new MEMRI method is sensitive to the negative effects of aging on AXT as well as microtubule-focused therapeutic strategies for improving AXT. Future studies will focus on OP effects/therapeutic strategies using this method which could have therapeutic implications for conditions that have been associated with repeated OP exposures, such as Gulf War Illness and Aerotoxic Syndrome.

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