EDITORIAL

Paraquat: The Red Herring of Parkinson’s Disease Research

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Definitions adapted from the American Heritage Dictionary

Red herring n 1: something that draws attention away from the central issue
n 2: a smoked herring having a reddish color (they turn red when cured)

Folklore suggests that criminals attempting to throw off pursuing bloodhounds would rub the fish across their trail

Definition from Monty Python and the Holy Grail

Herring n 3: an implement for felling mighty trees as suggested by misguided knights

After the discovery that 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) induced a parkinsonian syndrome in individuals who inadvertently injected the by-product of illicit drug manufacturing (Langston et al., 1983; Ramachandiran et al., 2007; Richardson et al., 2005), numerous investigators made the observation that the herbicide paraquat (N,N’-dimethyl-4,4’-bipyridinium dichloride, CAS# 1910-42-5) bore a degree of structural similarity to the active metabolite of MPTP, 1-methyl-4-phenylpyridinium (MPP⁺; CAS# 39794-99-5; see Fig. 1). Since that time, well over 100 papers have been published using paraquat as a cellular or animal model of Parkinson’s disease under the premise that the two compounds are structurally similar.

Direct injections of paraquat into the brain demonstrated its ability to damage the dopamine system and helped to identify some potential toxicological manifestations of the compound, but at the same time such studies largely ignored the physical obstacle presented by the blood-brain barrier and the complicated architecture of the brain (Barbeau et al., 1985; Corasaniti et al., 1992; Iannone et al., 1989; Liou et al., 1996). Indeed, it is intuitively obvious that an injection of a strong oxidant directly into nigral neurons or direct application to isolated mitochondria will cause damage, but is this toxicologically relevant? When paraquat is administered systematically, the results have been equivocal (Brooks et al., 1999; Corasaniti et al., 1992; McCormack et al., 2002; Widdowson et al., 1996). Some laboratories observe a consistent loss in nigral neurons (of no more than 25%), but not loss of striatal dopamine, which is considered a hallmark of the disease. Other laboratories have failed to demonstrate toxicity after systemic administration. In contrast, systemically administered MPTP kills a much higher percentage of the neurons (> 90%) and leads to a consistent loss of dopamine, both of which exhibit a clear dose response. Thus, while it does appear that after i.p. injection paraquat enters the brain of certain rodent species and strains, it is not clear if this is at all relevant to the human condition. Many of these widely cited studies, on which the ability of paraquat to damage dopamine neurons is based, are quite artificial from an exposure standpoint and only served to perpetuate the fishy and tenuous connection between the compounds.

In retrospect, evidence suggests that the aforementioned research efforts have been somewhat misguided. It has become a veritable dogma that since paraquat looks like MPP⁺ that it must act like MPP⁺ (coincidentally, the structure of the related cyperquat is truly identical to that of MPP⁺, see Fig. 1). Recent studies cast serious doubt upon this assertion. It has been assumed that paraquat is transported into the dopamine neuron by the dopamine transporter, like MPP⁺. Further, it has been assumed (and stated in numerous reviews) that paraquat is a complex I inhibitor. Recent data demonstrate neither to be physiologically plausible.

Studies using cell lines expressing the dopamine transporter reveal that paraquat is not transported via the dopamine transporter, nor does it impair dopamine uptake (Ramachandiran et al., 2007; Richardson et al., 2005). Paraquat can inhibit complex I, but only at an IC₅₀ of 7mM, which would be biologically impossible, especially given the fact that in actively respiring mitochondria paraquat does not display further accumulation. Meanwhile, MPP⁺ inhibits complex I in the 30μM range, which considering the ability of MPP⁺ to be specifically accumulated in the dopamine neuron by the dopamine transporter and that actively respiring mitochondria do accumulate the toxic compound, is indeed physiologically relevant (Richardson et al., 2005, 2007). For comparison’s sake, the lipophilic piscicide rotenone inhibits complex I in the low nanomolar range. While paraquat can induce redox cycling in the cytosol, which could alter mitochondrial function indirectly, the data suggest that when compared to MPP⁺ or rotenone, paraquat...
MPTP is converted in the brain to MPP\textsuperscript{+}, which is the same molecule as cyperquat. One of the pyridine rings of MPP\textsuperscript{+} and cyperquat is charged, whereas both of the pyridine rings are charged in the paraquat molecule.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structures.png}
\caption{Structures of MPTP, MPP\textsuperscript{+}, paraquat, and cyperquat. The lipophilic MPTP is converted in the brain to MPP\textsuperscript{+}, which is the same molecule as cyperquat. One of the pyridine rings of MPP\textsuperscript{+} and cyperquat is charged, whereas both of the pyridine rings are charged in the paraquat molecule.}
\end{figure}

Paraquat cannot be considered to be a physiologically relevant complex I inhibitor. In addition, paraquat has two positive charges, rendering it very different from a physical chemistry standpoint.

So does this mean that paraquat research has been a waste of time? No, this is not at all the case. Paraquat is a very efficient redox cycling compound. Since oxidative stress has been implicated in Parkinson’s disease, using an oxidant as a model toxicant in Parkinson’s disease research is reasonable. Furthermore, epidemiological evidence does support a connection between pesticide exposure and Parkinson’s disease, even though published epidemiological reports are unable to accurately identify specific compounds responsible for the association. Thus, it is still within the realm of possibility that paraquat could be involved in the pathogenesis of Parkinson’s disease, but such a connection must be established with epidemiological studies that can document exposure and discern between different classes of pesticides.

If we continue to cite this herring (structural similarity of paraquat and MPP\textsuperscript{+}), we may never identify the Holy Grail of the cause and cure of Parkinson’s disease, and our search may be as frivolous and futile as trying to chop down the mightiest tree in the forest with said fish (“Cut down a tree with a herring? It can’t be done”). Combining paraquat with other pesticides to model the disease has not brought any clarity to the field (Thiruchelvam et al., 2000). If anything, it may be another aromatic fish throwing us off the scent. Going forward, investigators need to properly identify paraquat as a compound that can be used to study oxidative damage to dopamine neurons and further explore the precise mechanisms by which it crosses the blood-brain barrier, gains access to the dopamine neuron, and causes the eventual destruction of a subpopulation of dopamine neurons. In the absence of this important mechanistic information and given the paucity of data demonstrating the plausibility of widespread human exposure, the link between paraquat and Parkinson’s disease should be viewed with a reasonable degree of skepticism. In the meantime, for the sake of scientific integrity, the phrase “Based on its structural similarity to MPP\textsuperscript{+}, paraquat . . .” or variations thereof should be banned from our vernacular.

**REFERENCES**


