Paraquat and Parkinson’s Disease: Response by Dr. Miller, Part II

Gary W. Miller

Center for Neurodegenerative Disease, Emory University, Atlanta, GA

Received February 5, 2008; accepted February 7, 2008

The letter by Dr LoPachin and Dr Gavin outlines several criticisms of my editorial “Paraquat: The Red Herring of Parkinson’s Disease Research (Miller, 2007).” The major issues noted include the lack of conclusive evidence that 1-methyl-4-phenylpyridinium (MPP+) exerts its toxic effects via complex I inhibition, my failure to recognize the importance of structure–activity relationships, and my failure to not cite evidence contradicting my views.

I have followed the work that has suggested alternate actions of toxicity of MPP+. I was especially intrigued by the report cited by LoPachin and Gavin suggesting that part of MPP+ toxicity may be due to disruption of vesicular storage of dopamine (Lotharius and O’Malley, 2000). However, a later report from the same group, which LoPachin and Gavin failed to cite, refuted the dopamine displacement hypothesis using intact animals engineered to be devoid of dopamine (Hasbani et al., 2005). Several alternate mechanisms of MPP+ toxicity have been suggested, but the evidence continues to point to complex I inhibition as being the most important. Has it been conclusively shown as the authors demand? Probably, no more conclusively than many other hypotheses surrounding neurodegeneration. I am not sure what more evidence I could provide to convince the authors of this, but the ability of genetic transfection of a rotenone-insensitive complex I ortholog to prevent in vivo toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine is just the most recent piece of evidence (Seo et al., 2006). The authors also cite another very recent paper that reports that complex I is the primary site of paraquat-induced superoxide formation (Cocheme and Murphy, 2008). Upon close examination, one sees that the low affinity transporter for paraquat across the mitochondrial membrane described in this report has an estimated affinity of 3mM (notably, this is not the same transport mechanism by which MPP+ crossed, adding yet another dissimilar activity). Although bathing isolated heart mitochondria in millimolar concentrations of paraquat shows some complex I–mediated toxicity, one must ask how relevant this heroic concentration of paraquat is to Parkinson’s disease pathogenesis? With regards to potential cumulative effects of paraquat, one only needs to peruse the studies from the DiMonte laboratory that show that paraquat does not exhibit cumulative toxicity, but rather a perplexing plateau of dopamine neuron cell loss (McCormack et al., 2005).

The next issue was that of the structure–activity relationship. There has been a great deal of emphasis on the structure component, but the authors seem to be ignoring the activity side of the relationship. If one examines several of the activities attributed to MPP+ toxicity (blood brain barrier penetration of parent compound, transport into dopamine neuron via plasma membrane dopamine transporter, binding to complex I, oxidation of specific cellular compartments, and mechanisms of cell death), it becomes quite apparent that these structurally similar compounds do not share similar activities. This was quite surprising to me as I do believe in the power of structure–activity based approaches in elucidating actions of various chemicals, but clearly for these critical steps in dopamine neuron damage these structurally similar compounds are not similar in their activities. It is certainly possible that these two compounds would act similarly in some molecular reaction vessel, but such an activity has yet to be described. The authors’ suggestion that paraquat may exert toxicity via cumulative addition of terminal proteins that accumulate over time appears to be inconsistent with the aforementioned findings of the DiMonte laboratory.

The authors seem dismissive of my reliance of a series of papers from my own laboratory in constructing my argument, but it should be noted that these studies were designed to directly compare the actions of three well recognized Parkinson’s disease-related toxicants (rotenone, paraquat, and MPP+). This allowed us to avoid many of the confounding issues that are faced when comparing studies from different laboratories and models. Secondly, partly due to generous support of our collaborators, we had access to some rather unique tools that allowed us to directly address these activities (inducible dopamine transporter expressing cells, assays for complex I binding, antibodies to cytoplasmic and mitochondrial thireodoxin, and viral constructs for the rotenone-insensitive yeast ortholog to complex I). If citing my own studies that were specifically designed to address these questions is biased, then I am guilty as charged.

My editorial, which was never intended to provide a balanced review of the literature, was written to bring my interpretation, as
uninformed, naïve, provocative, and cavalier as it has been suggested to be, to this area of research. I find it extraordinary that for every activity that we ascribe to MPP\(^+\), that paraquat does not share that same activity. This is the point that I have been trying to make. The apparent structural similarity of paraquat to MPP\(^+\) is not a sound foundation on which to pursue further studies on paraquat. This is especially true when one can cite the ability to paraquat to selectively kill dopamine neurons when systemically administered. Ironically, this premise was reached based on the mistaken structural similarity, but it was established nonetheless. LoPachin and Gavin suggest that further research to determine how paraquat interacts with nerve terminal proteins and membranes is warranted. I concur. However, please base the research on a defensible premise (paraquat kills a subset of substantia nigra dopamine neurons in mice) and not on one (structural similarity to MPP\(^+\)) that can be so readily eviscerated.

REFERENCES