Letter regarding: “Paraquat: The Red Herring of Parkinson’s Disease Research”

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We write this letter in response to the recent editorial entitled “Paraquat: the Red Herring of Parkinson’s Disease Research” by G. W. Miller. In our opinion, this editorial fails to appreciate that Parkinson’s disease (PD) is a complex disease with multiple interactive etiologic risk factors and that our current animals models, as imperfect as they may be (is there such thing as a “perfect” model?), are critical tools for elucidating the nature and interplay of these factors. The article attempts to support a point of view based on an outdated and incomplete presentation of the current status of the models. Some specific examples of shortcomings are elaborated below:

1. The main issue stressed by the editorial appears to be that the herbicide paraquat possesses toxic properties different than those of the known neurotoxicant 1-methyl 4-phenylpyridinium (MPP+). Differences between them, however, were pointed out more than 20 years ago (e.g., Di Monte et al., 1986) and should not detract from the fact that both the paraquat and the 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine/MPP+ models have been instrumental to our understanding of mechanisms of nigrostriatal degeneration (a critical neurodegenerative feature of human parkinsonism). It is quite possible that different pathways ultimately converge to trigger the neurodegenerative process of PD (Dauer and Przedborski, 2003). For this reason, the availability of multiple complementary models actually empowers our experimental investigations. There is no “gold standard” paradigm, as the editorial implies.

2. The editorial indicates that, when paraquat is administered systemically to rodents, neurodegenerative changes have been equivocal. To support this statement, four manuscripts are cited, all dated 2002 or earlier. However, the study of McCormack et al. (2002) was the first in which dopaminergic cells in the mouse substantia nigra were counted using a state-of-the-art stereological technique. This study reported a significant neuronal loss, a finding subsequently confirmed by many laboratories throughout the world (e.g., Choi et al., 2006; Fernagut et al., 2007; Ossowska et al., 2005; Peng et al., 2004, 2007; Thiruchelvam et al., 2005). Thus, that paraquat is capable of killing nigral dopaminergic neurons is not equivocal but rather a recognized (and reproducible) effect.

3. Another questionable statement of the editorial is that “Combining paraquat with other pesticides to model the disease has not brought any clarity to the disease.” As mentioned above, investigations into mechanisms by which risk factors may interplay in the pathogenesis of PD is critical for our understanding of such a complex disease. Studies conducted over the past few years not only have clearly demonstrated that combining risk factors can markedly enhance the nigrostriatal damage caused by paraquat, but have also elucidated potentially important mechanisms of interaction (e.g., Barlow et al., 2003, 2004; Cicchetti et al., 2005; Prasad et al., 2007; Thiruchelvam et al., 2000). For instance, treatment with the fungicide maneb synergistically enhances paraquat neurotoxicity in the adult animal, at least in part by increasing the amount of paraquat in brain and delaying its central nervous system clearance (Barlow et al., 2003). Similarly, the neurotoxic effects of paraquat have recently been reported to be augmented by neonatal iron exposure (Peng et al., 2007). These findings raise the important question of what other dietary, pharmacological or environmental exposures might act similarly to maneb, especially considering that exposure to mixtures of chemicals is the norm for humans.

4. Other examples of important studies looking at interactions between risk factors ignored by the editorial are the enhanced neurotoxicity of paraquat, alone or in combination with maneb, as a function of aging, and the augmenting effect of neuroinflammatory processes on paraquat-induced neurodegeneration (Purisai et al., 2007; Thiruchelvam et al., 2003). Interestingly, aging is an established risk factor for PD, and epidemiological evidence points to an association between inflammation and increased PD risk (Chen et al., 2005).

5. A final example of the major shortcomings of the editorial is the lack of reference to important studies showing changes in alpha-synuclein expression and aggregation in the paraquat mouse model (Manning-Bo˘g et al., 2002). Alpha-synuclein is a protein implicated in the pathogenesis of PD, and the paraquat model points to toxicant-alpha-synuclein
interactions as a potential mechanism for the development of alpha-synuclein pathology in PD. Recent studies have also used paraquat to study gene-environment interactions in a variety of PD models, including transgenic mice over-expressing alpha-synuclein and Drosophila mutants lacking DJ-1 function (DJ-1 is another gene/protein associated with human parkinsonism) (Fernagut et al., 2007; Meulener et al., 2005; Norris et al., 2007). Results of these studies show, for example, that paraquat administration increases alpha-synuclein aggregation in transgenic mice and that DJ-1 knockout flies are strikingly more sensitive to paraquat toxicity.

In summary, we do appreciate that editorials are often selected to be "provocative." However, provocative discussions should not be undertaken at the expense of scientific fairness and intelligent analysis of the status of a scientific field. Editorials may also present contrasting points of view from scientists who may differ in their interpretation of research issues. However, the article recently published in Toxicological Sciences only provides a limited personal view and does not add any new perspective to the field. For this reason, it does not serve the scientific community well.

REFERENCES


