Commentary on ‘Biochemical mechanism of action of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)’

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Since its discovery in a batch of an illicit street drug several years ago, the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has proved to be a very useful experimental model for in vitro and in vivo studies of Parkinson’s disease. A number of metabolic and biochemical events have been described or suggested to be involved in MPTP-induced neurotoxicity, including its metabolic activation by monoamine oxidase B (MAO-B) to form the putative toxic metabolite 1-methyl-4-phenylpyridinium ion (MPP+) via the 1-methyl-4-phenyl-2,3-dihydropyridinium species (MPDP+) [1], the uptake of MPP+ by the dopaminergic system of neurons [2], and the binding of MPP+ to neuromelanin within selectively damaged neurons [3].

Our interest in MPTP stemmed mainly from the fact that the generation of oxygen radicals had been implicated in its cytotoxic effects and that MPP+ had been suggested to resemble the bipyridynium herbicide paraquat (PQ2+) in generating these radicals via a mechanism of redox cycling with molecular oxygen. By using a cellular model system (which was manipulated in order to be more susceptible to the biochemical and toxic consequences of oxygen radical formation) we cast doubt upon the original hypothesis and concluded that: (a) PQ2+ and MPP+ caused cell death via different mechanisms [4]; (b) oxygen radical generation did not seem to be responsible for the cytotoxicity of either MPTP or MPP+ [5]; and (c) a dramatic depletion of cellular energy supplies in the form of ATP clearly preceded the onset of MPTP-
and MPP⁺-induced cell death [6]. The latter finding gave crucial support to the work of other investigators who had characterized the ability of MPP⁺ to inhibit mitochondrial respiration [7,8]. It is now generally accepted that depletion of ATP is a critical biochemical event leading to cytotoxicity after exposure to MPTP or MPP⁺. Indeed, the only effective 'antidote' against MPP⁺ toxicity to date has been found in compounds able to stimulate ATP production in the cytosol, thereby bypassing the mitochondrial inhibition [9].

Questions remain, however, concerning the role played by all of these biochemical events in the pathogenesis of Parkinson's disease. Presently, experimental evidence supporting a role for oxidative stress in MPTP toxicity is rather weak. Yet, two important considerations need to be made. Firstly, a number of toxic properties of MPTP/MPP⁺ have been characterized using different in vitro systems. No definitive evidence exists, however, of their involvement in the selective pathologic damage following MPTP exposure in vivo. Whether or not the vulnerability of the nigrostriatal system to MPTP is due to a specific mechanism of cytotoxicity (involving, for example, the high levels of dopamine and/or transition metals in the tissue) or to other peculiar factors (such as the accumulation and long-term retention of the neurotoxin) needs to be determined. Until then, and until the complete sequence of biochemical events which follow MPTP exposure and precede its neurotoxicity is mapped out, a role of oxidative stress as well as other toxic mechanisms cannot be excluded. Secondly, although MPTP has provided us with a remarkable model for Parkinson's disease, the distinction between MPTP-induced parkinsonism and the idiopathic disease should be taken into consideration – unless, of course, a neurotoxin(s) identical in mechanistic action is shown to be involved in the etiology of Parkinson's disease. Recent information derived from studies with MPTP support the hypothesis that an impairment of energy production by mitochondria may be involved in the pathogenesis of neurodegenerative disorders, thus opening a rather exciting area for future investigations. It would be unjustified, however, to neglect the fact that previous theories have focused attention on the role of oxidative processes, leading to irreversible cell injury, in the 'chronic' evolution of Parkinson's disease [10].

In light of the previous considerations it is evident that, no matter how challenging the research opportunities prompted by the discovery of MPTP in the past years have been, the most intriguing questions are still to be addressed. Investigations regarding the biochemical basis for the selective neurotoxicity of MPTP and its closeness to the idiopathic disease would certainly be fruitful.

An excellent example of the type of approach needed to address critical questions about MPTP toxicity is represented by the work of Dr. Sayre and his colleagues. As described in the following review, these investigators have characterized the mitochondrial damage caused by MPP⁺ and related analogs in vitro, and have then tested these analogs in vivo in order to correlate their biochemical properties with neurotoxic effects. Sayre concludes: 'in vivo neurotoxicity correlates most closely with in vitro respiratory inhibition exerted by these analogs on intact mitochondria'. In our opin-
ion, this work represents the most convincing evidence to date for the involvement of mitochondrial damage in the neurotoxicity of MPTP in vivo. On the other hand, the most controversial aspect of this group's work is their claim that MPP⁺ accumulation by mitochondria is a passive process rather than the active one proposed by other workers [8]. This is an important point, to which we draw your attention, and may provide a challenging area for future work.

REFERENCES