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Invited review

N-methyltetrahydropyridines and pyridinium cations as toxins and comparison with naturally-occurring alkaloids

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ABSTRACT

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 1-methyl-4-phenylpyridinium cation (MPP^+) are selective dopaminergic neurotoxins producing Parkinsonism. MPTP is activated by monoamine oxidase-B (MAO-B) to MPP^+ that inhibits mitochondrial function. Molecules resembling MPTP which afford pyridinium cations are also neurotoxins. The herbicide paraquat (a bipyridinium dication) and the naturally-occurring β-carboline and isoquinoline alkaloids are structural analogues of MPTP/MPP^+. Paraquat generates reactive oxygen species (ROS) producing neurotoxicity by a mechanism that differs from MPTP/MPP^+. Human exposure to PQ is increasingly associated with neurodegeneration. Tetrahydro-β-carbolines (THβCs), β-carbolines (βCs) and tetrahydroisoquinolines (TIQ_s) are bioactive compounds occurring in foods and the human body. They are not MPTP-like toxins and do not appear to induce neurotoxicity at normal levels of exposure. Among TIQs, endogenous dopamine-derived TIQs (*i.e.* salsolinol) and 1-benzyl-TIQ are toxic through ROS generation. In contrast, β-carbolinium (βC^+s) and isoquinolinium cations (IQ^+s) are neurotoxicants resembling MPP^+ although they are less potent and selective. βC^+s and IQ^+s have been detected in the human brain but their toxicological significance remains unknown. THβCs/βCs and TIQs are activated to toxic cations by *N*-methyltransferases (NMT) and/or heme peroxidases and are metabolized by cytochrome P450 enzymes. Remarkably, recent findings suggest, instead, that βCs and TIQs are neuroprotectants and neurorestorative, raising the interest of these molecules.

Contents

List of abbreviations: BBB, blood-brain barrier; βCs, β-carbolines; βC^+s, β-carbolinium cations; CSF, cerebrospinal fluid; CYP, cytochrome P450; DAT, dopamine transporter; IQ^+s, isoquinolinium cations; LPO, lactoperoxidase; MPO, myeloperoxidase; MAO, monoamine oxidase; 2-Me-βC^+, 2-methyl-β-carbolinium cation; 2,9-diMe-βC^+, 2,9-dimethyl-β-carbolinium cation; 9-Me-βC, 9-methyl-β-carboline; $MPDP^+$, 1-methyl-4-phenyl-2,3-dihydropyridinium cation; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+, 1-methyl-4-phenylpyridinium cation; 1-Me-TIQ, 1-methyl-1,2,3,4-tetrahydroisoquinoline; NMT, *N*-methyltransferase; RNS, reactive nitrogen species; ROS, reactive oxygen species; PD, Parkinson's disease; PQ, paraquat; THβCs, 1,2,3,4-tetrahydro-β-carbolines; TIQs, 1,2,3,4-tetrahydroisoquinolines; SAM, *S*-adenosyl-L-methionine; SNpc, *substantia nigra* pars compacta.

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1. Introduction

Chemical substances containing *N*-methyltetrahydropyridine and *N*-methylpyridinium moieties are presumably neurotoxins. A paradigmatic example is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Fig. 1) that produces idiopathic Parkinson's disease (PD) in animals and humans. Neurotoxicity is triggered by 1-methyl-4-phenylpyridinium (MPP^+) metabolite which is generated in the brain from MPTP. Both MPTP and MPP^+ (if administered directly in the brain) induce experimental Parkinsonism in animal models and these neurotoxins are extensively used to investigate the mechanisms underlying neurotoxicity and neurodegeneration and to find neuroprotectant drugs (Jackson-Lewis and Przedborski, 2007). PD is a neurodegenerative disorder characterized by a progressive and selective loss of dopaminergic neurons but the exact cause of this loss remains unknown. The discovery of MPTP/MPP^+ as neurotoxins have raised questions on the safety of other tetrahydropyridines and pyridinium substances and has stimulated the research on environmental or endogenous agents potentially involved in neurotoxicity (Castagnoli et al., 1997). Drugs containing *N*-alkyltetrahydropyridine moieties such as haloperidol and loperamide are metabolized to potentially toxic pyridinium compounds (Kalgutkar and Nguyen, 2004; Usuki et al., 1996) (Fig. 2). Patients treated with haloperidol, a neuroleptic agent, often experience extrapyramidal side effects including dystonic reactions and Parkinsonism. Popular pesticides which are bipyridinium cations like paraquat (PQ) (Fig. 1) have been largely characterized as toxic substances, and more recently also as neurotoxicants (Baltazar et al., 2014). Epidemiological and experimental studies have increasingly suggested the involvement of PQ in neurodegenerative diseases (Kamel, 2013). Human exposure to

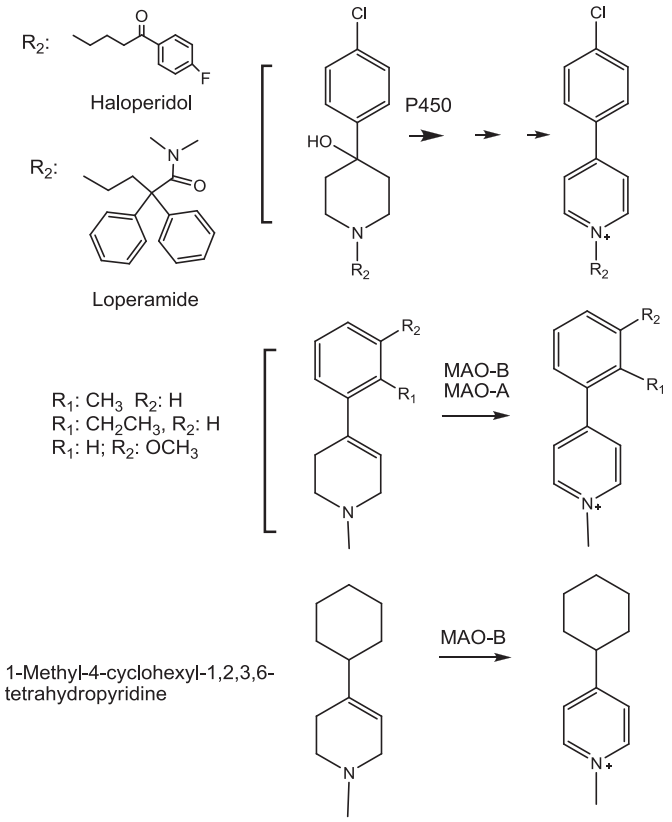

Fig. 2. Drugs haloperidol and loperamide containing *N*-alkyltetrahydropyridine moieties that are activated by CYP enzymes to potentially toxic pyridinium cations. Neurotoxic analogues of MPTP that are activated by MAO enzymes to toxic pyridinium cations.

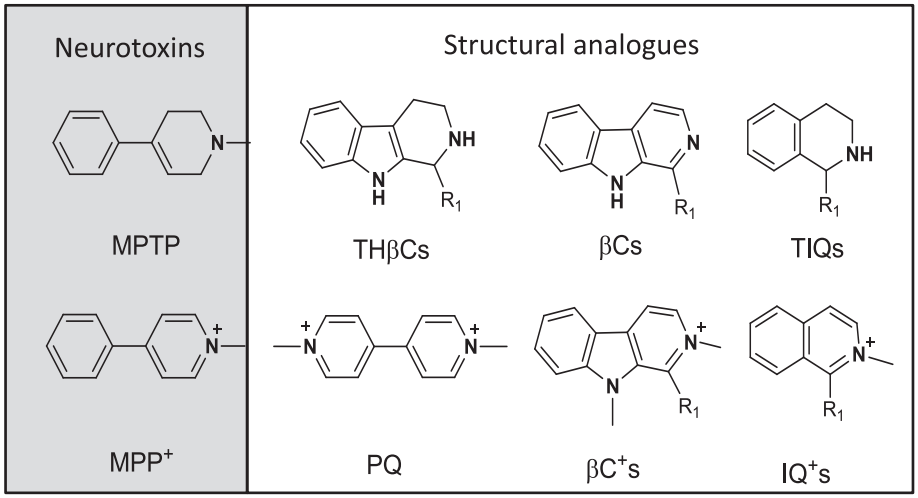

Fig. 1. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and MPP^+ (1-methyl-4-phenylpyridinium cation) neurotoxins and structural analogues: paraquat (PQ) (1,1′-dimethyl-4,4′-bipyridinium dichloride), tetrahydro-β-carbolines (THβCs), β-carbolines (βCs), tetrahydroisoquinolines (TIQs), and β-carbolinium (βC^+s) and isoquinolinium cations (IQ^+s).