may, however, give a reasonable prediction of *intrinsic* ulcerogenicity of NSAI drugs.

(5) Dearden & Nicholson used carrageenan-injected rats in their combined study of ulcerogenicity and anti-inflammatory activity, a model originally developed by Rainsford & Whitehouse (1977). While that acute assay method might have advantages in reducing the cost and numbers of animals (as was originally noted), the large quantity of prostaglandins (PGs) released into the circulation from the injected paws could be sufficient to act as systemic cytoprotective agents despite some lung metabolism of these PGs. Such protection could account for the lower IC50 values obtained, in comparison with those of Rainsford, for the more potent prostaglandin synthesis inhibitors, i.e. aspirin, diclofenac, flubiprofen, indomethacin, naproxen, phenylbutazone, piroxicam and tolmetin.

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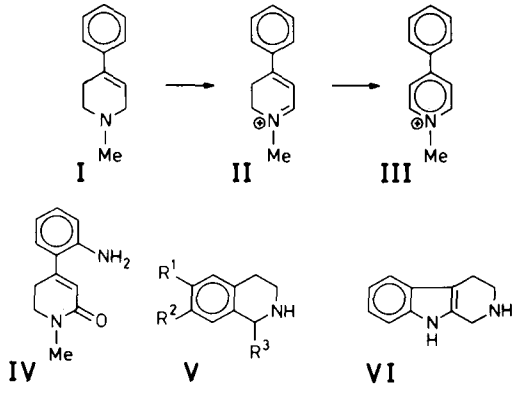
Does an endogenous methylpyridinium analogue cause Parkinson's disease?

B. TESTA*, R. NAYLOR†, B. COSTALL†, P. JENNER‡, C. D. MARSDEN‡, *School of Pharmacy, University of Lausanne, Place du Chateau, CH-1005, Lausanne, Switzerland, †Postgraduate School of Studies in Pharmacology, University of Bradford, Bradford BD7 1DP, UK, ‡MRC Movement Disorders Research Group, University Department of Neurology and Parkinson's Disease Society Research Centre, Institute of Psychiatry and King's College Hospital Medical School, Denmark Hill, London SE5, UK*

Parkinson's disease affects 1 in 1000 of the general population, and its incidence increases with age, but its cause remains unknown. Twin studies suggest that hereditary factors are not involved (Duvoisin et al 1981). To try to explain the death of dopamine neurons in the brain, the major pathological change in Parkinsonism, attention has been focused on environmental agents or endogenous toxins.

The peripheral administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, I) produces persistent Parkinsonism in human addicts due to selective destruction of the dopamine-containing cells of substantia nigra in brain (Langston et al 1983; Burns et al 1983). The molecular mechanisms underlying this effect are not fully understood, but it is established that MPTP is metabolized by monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$, II) and then converted to 1-methyl-4-phenylpyridinium (MPP^+, III) (Markey et al 1984; Gessner et al 1984). MPTP-induced toxicity in primates and rodents is prevented by pretreatment with selective MAO-B inhibitors such as deprenyl (Langston et al 1984; Heikkila et al 1984). However, other compounds similar to MPTP may be present in the environment. MPTP itself is not an endogenous molecule nor does it occur naturally in the environment. Another possibility is that some natural toxicant resembling MPTP may be formed endogenously.

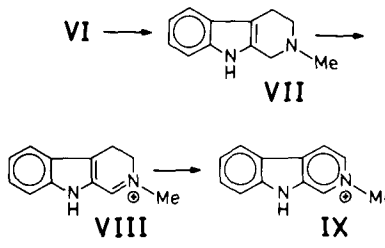


With this idea in mind, Ramsden & Williams (1985) proposed a metabolic sequence leading from tryptamine to compound IV, a hypothetical endogenous MPTP-like toxicant. While the proposal has merit, compound IV is not 'a strong contender for the structure of the toxic oxidation product of MPTP . . .' (Ramsden & Williams 1985). Indeed, the postulated metabolic sequence involves some improbable steps such as the *N*-acetylation of a secondary amine, and especially condensation following a nucleophilic attack by a poorly reactive

* Correspondence.

carbon atom. Additionally, no explanation is offered as to how the lactam IV, with its neutral character and reduced electronic conjugation (conformational ortho effect of the amino group), can mimic the critical structural properties of $MPDP^+$ and MPP^+.

We believe that other compounds are more likely to be contenders for being endogenous MPTP-like compounds. In a recent review, we (Mesnil et al 1984) discussed how catecholamines and tryptamines react in-vivo with carbonyls to yield tetrahydroisoquinolines (TIQs, V) and tetrahydro-β-carbolines (THBCs, VI) respectively. Representative derivatives are salsolinol (V, $R^1 = R^2 = OH$, $R^3 = Me$) formed from dopamine and acetaldehyde, and THBC (VI) formed from tryptamine and formaldehyde.



A critical step in the activation of endogenous derivatives V and VI should be a reaction of *N*-methylation, since we have evidence (Bradbury et al 1985) that analogues of MPTP and MPP^+ lacking a *N*-methyl group are essentially devoid of toxicity. Numerous endogenous compounds undergo methylation of an endocyclic or exocyclic nitrogen atom by such enzymes as phenylethanolamine *N*-methyltransferase (PNMT), histamine *N*-methyltransferase, or indolethylamine *N*-methyltransferase. Xenobiotics undergoing *N*-methylation in brain and/or other tissues by these or other enzymes include theophylline, normorphine and pyridine, among a number of other heterocyclic compounds (for reviews see Testa & Jenner 1976; Borchardt 1980; Caldwell 1982; Mesnil et al 1984).

Compounds V and VI, after *N*-methylation to yield, e.g. the postulated derivative VII, would indeed be close analogues of MPTP. Their conversion to methylpyridinium derivatives requires two steps, namely formation of an iminium cation and α-β-dehydrogenation. This is the sequence believed to occur in MPTP activation and which will be considered below. It is also conceivable, however, that α-β-dehydrogenation precedes iminium ion formation.

Iminium ion formation (e.g. the generation of VIII) could be MAO-mediated as is the case for MPTP, or it could be catalysed by monooxygenases as is the case for, e.g. nicotine (Nguyen et al 1979) and phencyclidine (Ward et al 1982). The second step in MPTP activation, namely aromatization leading from II to III, may also involve MAO-B although the rate is slow (Gessner et al 1984). Because of this relative inefficiency, involvement of cytochrome P-450 is a distinct possibility. The same considerations are valid e.g. for the aromatization of the postulated endogenous intermediate VIII to IX. Such postulates are testable by means of in-vitro metabolic studies of *N*-methylated TIQs and THBCs, which should reveal the relative roles played by MAO and cytochrome P-450.

The postulated existence of an endogenous parkinsonism-causing toxicant closely related to MPP^+ is compatible with the apparent protection experienced by cigarette smokers. Indeed, a negative correlation exists between the incidence of Parkinson's disease and the degree of cigarette smoking, although the reasons are not understood (Bauman et al 1980). It may be that nicotine, a *N*-methyl alicyclic amine, is also a substrate for cerebral MAO giving rise to an iminium ion previously shown to be produced in hepatic microsomal preparations (Nguyen et al 1979). Nicotine could competitively inhibit the activation of *N*-methylated TIQ's and THBC's by MAO.

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