Tetrahydroisoquinoline lacks dopaminergic nigrostriatal neurotoxicity in mice

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1,2,3,4-Tetrahydroisoquinoline (TIQ) has been reported to occur in human brain, with its content being 10-fold higher in the brain of a patient with Parkinson’s disease (PD) than in that of a control subject. This congener of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) could be formed in brain by the condensation of phenylethylamine with metabolically formed formaldehyde. Phenylethylamine contents are greatly increased in the tissues of untreated patients with phenylketonuria. We injected C57 black mice repeatedly with maximal tolerated doses of TIQ, but later found no reduction in the contents of dopamine and its metabolites in their striata. We doubt that TIQ is a cause of PD, especially since the disorder has not been reported to occur in elderly patients with phenylketonuria.

The discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can produce neuropathological and neurochemical changes resembling those of idiopathic Parkinson’s disease (PD) in humans, monkey and mice [8] has stimulated a large number of studies of MPTP and its analogues in a search for possible causes of idiopathic PD. The effects of MPTP and its neurotoxic mechanisms have recently been reviewed by Kindt et al. [6] and Singer et al. [16]. Calne and Langston [1] suggested that PD may be caused by progressive damage to dopaminergic nigrostriatal neurons by one or more unidentified environmental toxins, which might or might not resemble MPTP chemically. On the other hand, Eldridge and Rocca point out that age-specific incidence rates for PD have remained stable for the last half century, and that incidence rates according to country do not indicate any consistent pattern [2]. These epidemiologic observations suggest that idiopathic PD may not be caused by an environmental agent, at least not by one of infrequent and irregular occurrence.

Congeners of MPTP, formed endogenously by the condensation of biogenic amines with formaldehyde or acetaldehyde, are possible neurotoxins which should...
be considered in searching for the causes of idiopathic PD. Such endogenous compounds include the tetrahydro-β-carbolines formed from tryptamine and serotonin [4], and the tetrahydroisoquinolines formed from phenylethylamine and dopamine [17]. The N-methylisquinolinium ion, for instance, has been found to inhibit tyrosine hydroxylase in rat striatum in vitro [5]. Niwa et al. recently reported identifying 1,2,3,4-tetrahydroisoquinoline (TIQ) and 2-methyl-1,2,3,4-tetrahydroquinoline (Me-TQ) in human brain using a gas chromatographic–mass spectrometric technique [10]. They found more than 10 times as much TIQ in the autopsied brain of a patient with PD as in the brain of a non-neurological control patient, while content of Me-TQ were similar in the two brains. TIQ could be formed in brain from phenylethylamine by condensation with active formaldehyde, or from phenylalanine, with subsequent decarboxylation. We have therefore tested authentic TIQ for possible dopaminergic nigrostriatal neurotoxicity in C57 black mice, a rodent strain in which these neurons are readily damaged by MPTP [14].

TIQ (Aldrich) was dissolved in 0.9% NaCl and converted to its hydrochloride salt by addition of HCl, after which the solution was adjusted to pH 6.5. Female C57 black mice, aged 3½ months at the start of the experiment, were given s.c. injections of TIQ daily 5 times a week for a total of 19 injections over a 26-day period. Dosage was increased progressively from 60 to 150 mg/kg (calculated as the free base). Mice exhibited sedation for a short period after injections with doses of 80 mg/kg or higher, and had tremor and clonic convulsions immediately after doses of 150 mg/kg. However, TIQ-treated mice gained weight as well as did untreated litter-mate controls, and differed from them only in being markedly overactive.

Five weeks after the last TIQ injection, mice were killed by cervical dislocation. The striata were dissected out immediately, weighed, then frozen at ~70°C until analysed. Contents of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were measured simultaneously in striatal homogenates by high-performance liquid chromatography with electrochemical detection [13].

Table I shows the mean contents of dopamine and its metabolites in striata of con-

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**Table I**

<table>
<thead>
<tr>
<th>Cumulative dose (mg/kg)</th>
<th>Dopamine</th>
<th>DOPAC</th>
<th>HVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (10)</td>
<td>16.54 ± 0.32</td>
<td>0.94 ± 0.05</td>
<td>1.37 ± 0.07</td>
</tr>
<tr>
<td>TIQ (10)</td>
<td>2120</td>
<td>16.15 ± 0.56</td>
<td>0.87 ± 0.05</td>
</tr>
</tbody>
</table>

Values (mean ± S.E.M.) expressed in μg/g wet wt. Number of animals shown in parentheses. Mice were given a total of 19 s.c. injections of TIQ over a period of 26 days. Dosage was increased progressively from 60 to 150 mg/kg (calculated as the free base). Mice were sacrificed 5 weeks after the last injection. None of the experimental values differs significantly from the controls.
trol mice and of litter mates injected repeatedly with TIQ in a cumulative dose of 2120 mg/kg. Dopamine contents were not reduced by this massive chronic exposure to TIQ.

Our results do not agree with those of Nagatsu and Hirata [9] who reported tyrosine hydroxylase enzyme activity reduced in the striata of mice given less than one fourth the total amount of TIQ that we used. We have previously shown that 2-methyl-1,2,3,4-tetrahydro-6,7-isooquinolinediol, a tetrahydroisoquinoline which might be formed endogenously from dopamine, lacks dopaminergic nigrostriatal neurotoxicity in the mouse [12]. In addition, 2-methyl-1,2,3,4-tetrahydroisoquinoline and 2-methyl-1,2,3,4-tetrahydro-β-carboline failed to damage these neurons in mice [15] and in marmosets [11] after repeated injections. Gibb et al. [3] have shown that a number of tetrahydro-β-carbolines and tetrahydroisoquinolines are not substrates for monoamine oxidase B, the enzyme which converts the precursor MPTP into the active neurotoxin N-methyl-4-phenylpyridinium ion. This may explain why the 3 tetrahydroisoquinolines which we tested have all failed to damage dopaminergic nigrostriatal neurons.

It is possible, of course, that TIQ might damage these neurons in man and produce idiopathic PD as Niwa et al. [10] suggest, while exhibiting no such neurotoxicity in mice. This seems unlikely to us, however, when one considers that untreated patients with phenylketonuria have brain contents of phenylethylamine and phenylalanine, both precursors of TIQ, which are enormously and chronically elevated [7]. To our knowledge, there has been no report of increased occurrence of PD in such untreated elderly phenylketonuria patients.

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9 Nagatsu, T. and Hirata, Y., Inhibition of the tyrosine hydroxylase system by MPTP, l-methyl-4-phenylpyridinium ion (MPP+) and the structurally related compounds in vitro and in vivo, Eur. Neurol., 26 Suppl. 1 (1987) 11–15.


