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Author(s)	OHTA, Shigeru
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CANDIDATES FOR PARKINSON'S DISEASE CAUSING SUBSTANCES

Shigeru OHTA

*Department of Bioorganic and Medicinal Chemistry,
Faculty of Pharmaceutical Sciences,
University of Tokyo, 7-3-1 Hongo, Bunkyo-Ku, Tokyo 113 Japan*

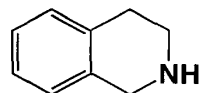
Recently there have been many reports in which 1, 2, 3, 4-tetrahydroisoquinoline (TIQ) derivatives may be related to the onset of Parkinson's disease. We have already confirmed that TIQ and 1-methyl-TIQ (1MeTIQ) were detected in the brains of mice, rats, and humans; and the 1MeTIQ content in the parkinsonian brain was decreased in comparison with that in a normal subject's brain, though the TIQ content was not changed in between both brains. In addition, pre treatment with 1MeTIQ perfectly prevented mice treated with TIQ or 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) from bradykinesia, one of the characteristic symptoms in Parkinson's disease. The slight difference in the structure between 1MeTIQ and TIQ, which is whether it has a methyl group at one position or not, induces a reverse effect.

On the other hand, Sandler et al. found tetrahydropapaveroline (THP) in the urine of parkinsonians treated with L-dopa. THP has an inhibitory activity to Complex I, one of the key components of the respiratory chain, and its toxic properties are similar to those of 1-methyl-4-phenylpyridinium ion (MPP⁺). THP also has a TIQ-skeleton, and it is formed from the condensation of dopamine and 3, 4-dihydroxyphenylacetaldehyde, a metabolite of dopamine by monoamine oxidase (MAO). Therefore, it was proposed that the condensation of 2-phenylethylamine (PEA) and its metabolite by MAO, phenylacetaldehyde, would lead to the formation of 1BnTIQ.

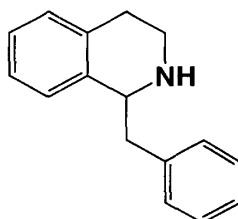
On the basis of our hypothesis, we could detect 1BnTIQ from the mouse brain, therefore, it was regarded as an endogenous amine in mouse brain. The same conditions were next used in the detection of 1BnTIQ in human CSF. The content of 1BnTIQ in parkinsonian CSF was 1.17 ± 0.74 ng/ml CSF (mean \pm S.E.M.; n=18) and that in normal subjects' CSF was 0.40 ± 0.23 ng/ml CSF (mean \pm S.E.M.; n=11). The difference in content between both groups was not statistically significant. The R/S ratio of 1BnTIQ, which was derivatized to (-)-PPP adduct in the detection, was 1.03 in the mouse brain. Therefore, 1BnTIQ does not exist as the optically active form in the mouse brain.

In addition, 3', 4'-dihydroxy-1BnTIQ and 6, 7-dihydroxy-1BnTIQ were also detected in mouse brain. It is anticipated that cross condensation of dopamine or PEA with their respective metabolites would lead to the formation of these two compounds.

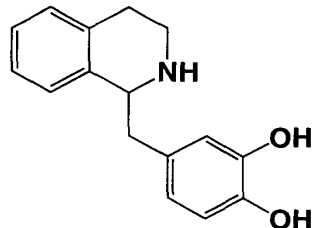
Parkinsonism causing substances



TIQ

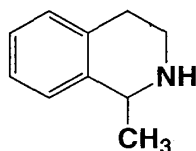


1BnTIQ



3',4'-dihydroxy-1BnTIQ

Parkinsonism preventing substance



1MeTIQ

In order to investigate the toxicological effect of TIQ derivatives, the pole test was tried. As the result, repeated administration of TIQ, 1BnTIQ and 3', 4'-dihydroxy-1BnTIQ induced bradykinesia, one of typical behavior abnormalities concerned with Parkinson's disease. It is assumed that compounds with a TIQ skeleton are closely related to the pathogenesis of Parkinson's disease.

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