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ROLE OF DOPAMINE METABOLISM IN NEUROPROTECTION AND NEUROTOXICITY OF ENDOGENOUS TETRAHYDROISOQUINOLINES.

Antkiewicz-Michaluk L. R. (1), Bojarski A. (2), Romanska I. (1) & Karolewicz B. (3)
(1) Lab. Rec. Neurotransm. Res. Biochemistry Dep. IF PAN, Kraków, Poland; (2) Med. Chemistry Dep. IF PAN, Kraków, Poland; (3) Lab. Rec. Neurotransm. Res. Biochemistry Dep. Kraków, Poland

Several of 1, 2, 3, 4-tetrahydroisoquinoline derivatives present in the brain are endogenous. In the present study we investigated the biochemical effects of potentially neuroprotective 1MeTIQ, and neurotoxic 1BnTIQ administered in a single dose or chronically on two pathways of dopamine catabolism: oxidative MAO-dependent pathway and O-methylation COMT-dependent pathway. Additionally, the neuroprotective effect of 1MeTIQ in rotenon treated rats was investigated. Rotenon is a common used pesticide, egzogenous neurotoxin producing similar to MPTP parkinsonian-like syndrome in rodents. However, there have been no studies of the effect on central dopamine metabolism and catabolic pathways after systemic administration of rotenone. The experiments were made on male Wistar rats. 1MeTIQ and 1BnTIQ were administered in dose (25, 50 mg/kg ip) once or daily for 17 days. Rotenon (10 mg/kg s. c.) once or daily for 7 consecutive days. Dopamine (DA) and its metabolites, homovanillic acid (HVA), 3, 4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine (3MT), were assayed by means of high-performance liquid chromatography (HPLC) with electrochemical detection in extrapyramidal (substantia nigra, striatum) and limbic (nucleus accumbens) structures. The results have shown that 1MeTIQ and 1BnTIQ produced different effects on DA catabolism in investigated structures. 1BnTIQ produced the significant increase of the rate of DA metabolism with strong activation of the oxidative MAO-dependent catabolic pathway. In contrast, 1MeTIQ did not change the total DA metabolism, but strogly inhibited the oxidative MAO-dependent catabolic pathways and significantly activated the COMT-dependent 0-methylation and, completely antagonized the increase of DA metabolism produced by rotenone in the rat striatum. The results may explain the biochemical basis of neuroprotective and neurotoxic properties of endogenous tetrahydroisoquinolines.