BRAIN MONOAMINE OXIDASE IN SCHIZOPHRENIA

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Monoamine oxidase (MAO) is a lipid-dependent thiol enzyme [9, 11]. The close connection between the protein and lipid parts of these enzymes is the reason why their properties are more closely dependent on lipid peroxidation (LPO) processes [1]. Although stimulation of LPO is observed in patients with schizopherenia, especially in the brain tissues [5], brain MAO activity of schizophrenic patients is unchanged compared with its activity in persons not suffering from this disease [6]. However, the published data were obtained by the investigation of unpurified MAO preparations, without fractionation of the many different forms of this enzyme. Under those circumstances, the property of MAO of undergoing reversible change of substrate specificity, induced by oxidation of protein SH-groups [4], also was disregarded.

In the investigation described below MAO activity was compared in normal subjects and schizophrenics, by the use of the principal form of partially purified human brain MAO, namely MAO IIb [3]. The specificity of the enzyme also was studied under conditions either favoring oxidation of protein SH-groups or, conversely, favoring their reduction.

EXPERIMENTAL METHOD

Brain tissue from subjects with no diagnosed disturbance of CNS functions (six subjects) and dying from cardiovascular diseases, was obtained from the mortuary of the I. M. Sechenov First Moscow Medical Institute. Brain tissues from persons suffering from schizophrenia during life and dying from cardiovascular diseases was obtained from the mortuary of the Institute of Clinical Psychiatry, All-Union Mental Health Research Center, Academy of Medical Sciences of the USSR. In all cases tissue from the cerebral cortex was obtained 4-19 h after death and kept at −20°C. MAO activity was judged from the quantity of liberated ammonia [3]. Concentrations of protein and thiol groups were determined by standard methods [7, 8].

EXPERIMENTAL RESULTS

The results of a comparative study of the properties of MAO IIb, isolated from the brain of schizophrenic patients and of persons not suffering from the disease (normal), show that the enzyme preparations deaminated not only serotonin (5-HT) and β-phenylethylamine (PEA), but also histamine (H), the substrate of diamine oxidase (Table 1). These MAO preparations were in the "oxidized" form: They contained about two SH-groups per 10^5 daltons (D) of protein; unoxidized MAO contains 14-15 SH-groups per 10^5 D of protein [10]. Incubation of the enzyme preparations at 37°C for 180 min (under aerobic conditions) normally reduced deamination of 5-HT and PEA but potentiated deamination of H with no change in the content of SH-groups. In schizophrenia, incubation under these same conditions led to a decrease only in deamination of PEA. Incubation of the enzyme preparation under the same conditions, but in the presence of the reducing agent dithiothreitol (DTT), normally considerably increased the number of SH-groups (up to 15) and also increased the velocity of deamination of PEA and 5-HT, but sharply reduced the velocity of deamination of H. Incubation of enzyme preparations from the schizophrenic brain in the presence of DTT revealed significant differences compared with normal in experiments with deamination of H: The velocity of this reaction after reduction with DTT to 15 SH-groups not only did not decrease, but on the contrary, it increased considerably.

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TABLE 1. Determination (in nanomoles NH_3/mg protein/min) of 5-HT, PEA, and H in Preparations of MAO IIb from the Brain of Schizophrenics (above the line) and Nonschizophrenics (below the line) (M ± m)

Conditions of preincubation	5-HT	PEA	H
Control	1,50±0,07 (4) 3,65±0,15 (8)	18,20±0,27 (4) 20,70±0,25 (11)	1,70±0,17 (4) 1,8±0,25 (5)
3 h, 37 °C	1,10±0,13 (4) 6,70±0,08 (5)*	7,6±0,4 (4)* 8,3±0,5 (8)*	2,0±0,3 (3) 3,5±0,4**
The same + 10 mM DTT	1,25±0,01 (4) 1,10±0,24 (4)*	11,1±0,3 (4)* 15,9±0,6 (8)*	0,50±0,55 (4)** 0,80±0,17 (5)*

Legend. *P < 0.001, **P < 0.01. Number of investigations in parentheses.

In previous experiments with purified MAO preparations from the bovine brain stem, high lability of their thiol groups was demonstrated: They readily underwent reoxidation on keeping [4, 10]. This was accompanied by broadening of their substrate specificity: In the oxidized state the enzyme deaminated many nitrogeneous compounds which are not MAO substrates (H, GABA, diamines, etc.) with high velocity. In the reduced state this property is lost or drastically diminished, in full agreement with the results of the present investigation. In schizophrenia, however, reduction of the enzyme not only did not reduce deamination of H but, on the contrary, increased it. This phenomenon was observed in experiments with brain MAO from all schizophrenics studied, irrespective of age, sex, and the character of the methods of treatment used. It can be tentatively suggested that in schizophrenia a definite change is observed in the structure of the brain MAO. This is indirectly supported not only by disturbances of the catalytic properties of the enzyme, described above, but also by determination of the number of SH-groups of the enzyme in the absence of urea. The value obtained under normal conditions was 40% less than that determined in the presence of urea. However, urea did not affect the number of SH-groups of the enzyme isolated from the brain of schizophrenics.

The results of this investigation indicate definite changes in MAO in schizophrenia, as a result of which deamination of histamine in brain tissues may be potentiated (without preliminary methylation). The histaminergic system of the brain is known to be disturbed [12] in this disease. The use of inhibitors of this oxidized form of MAO [2] in schizophrenia may prove to be an effective approach to the treatment of this disease.

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