Cathepsin K and Metabolic Abnormalities in Schizophrenia

To the Editor:

We read with much interest in the September issue of Arteriosclerosis, Thrombosis, and Vascular Biology the article by Yang et al entitled “Deficiency and Inhibition of Cathepsin K Reduce Body Weight Gain and Increase Glucose Metabolism in Mice.” The authors demonstrate a direct participation of cathepsin K (CatK) in mouse body weight gain and glucose metabolism. Furthermore, a strong increase in CatK mRNA was found after adipogenesis of human preadipocytes, whereas inhibition of CatK activity blocked the lipid accumulation in human and mouse preadipocytes. Thus, this study suggests an essential role of CatK in adipogenesis and body weight gain. These data are exciting with regard to the well-known yet poorly understood side effects of neuroleptic treatment of individuals with schizophrenia. Long-term treatment with atypical (and, to a lesser extent, typical) neuroleptics is frequently accompanied by the development of the “metabolic syndrome,” which is characterized by visceral obesity, type 2 diabetes, elevated lipid levels and hypertension, and decreased sensitivity to insulin, and which is the main cause for incompliance of the patients (for review see Sacks2).

Recently, it was found that the cath K gene belongs to the very few ones, which are linked to schizophrenia, are downregulated in its expression by the psychotropic substance amphetamine, but are upregulated by typical and atypical neuroleptics. In studies on postmortem brains of schizophrenics we could show that, compared to control cases, there is a significant increase in cerebral catK protein expression in the CNS of chronic schizophrenics who had received long-term treatment with neuroleptics. The consequences of this finding were not very clear to us at that time. We speculated that there might be implications on the cerebral opioid metabolism in schizophrenia (which has now been substantiated in a series of new experiments) and on bone metabolism of the patients. Now, the recent data of Yang and colleagues on the putative role of catK in adipocyte metabolism add an unforeseen aspect to the complex issue of possible consequences of upregulated catK activity in schizophrenia, namely its putative contribution to metabolic abnormalities. Undoubtedly, adipose tissue reacts in many ways on chronic neuroleptic treatment to enhance adiposity (for review see Cooper et al5). However, the newly discovered substantial role of the cysteine protease catK in lipid and glucose metabolism, together with the known metabolic complications observed in schizophrenia after neuroleptic treatment, bring about a testable hypothesis on its pathophysiologic function in that (1) an upregulation of catK expression should also take place in extracerebral tissues and bodily fluids (including adipose tissue) of chronic schizophrenics during/after medication, and (2) selective inhibition of the enzyme should lead to a certain “normalization” of the deviant lipid and glucose metabolism. However, the latter aspect should certainly be tested in an animal paradigm. If so, inhibition of catK might be a promising new tool to counteract the medication-induced metabolic complications in schizophrenia.

Disclosures

None.

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