SREBP Activation by Antipsychotic- and Antidepressant-Drugs in Cultured Human Liver Cells: Relevance for Metabolic Side-Effects?

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Abstract Drug-induced weight gain is a major problem in the treatment of psychiatric disorders, especially with some antipsychotic- and antidepressant drugs. We have recently demonstrated that antipsychotic- and antidepressant drugs activate the SREBP (sterol regulatory element-binding proteins) transcription factors in human- and rat glial cells, with subsequent up-regulation of downstream genes involved in cholesterol- and fatty acid biosynthesis. Since stimulation of cellular lipogenesis in the liver could be of relevance for the metabolic side effects of these drugs, we have now investigated the effects of antidepressants, antipsychotic- and mood-stabilizing drugs on cell cultures of human liver cells. For several of the drugs being strongly associated with weight gain (clozapine, imipramine, and amitriptyline), we observed a very pronounced activation of SREBP. Ziprasidone and buproprion, however, which are not associated with weight gain, did hardly stimulate the SREBP system. For haloperidol, olanzapine and mirtazapine, the correspondence between metabolic side effects and SREBP stimulation in liver cells was less obvious. The mood-stabilizers did not increase SREBP activation. The results indicate a relationship between drug-induced activation of SREBP in cultured human liver cells and weight gain side-effects of antidepressant and antipsychotic drugs.

Key words antidepressants - antipsychotics - mood-stabilizers - side-effects - weight gain - mechanism