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A NOVEL MECHANISM OF OLANZAPINE-INDUCED LIPID ACCUMULATION

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Introduction: Second generation antipsychotic drugs (SGADs) including olanzapine trigger adverse metabolic alterations possibly by a direct action on adipocytes.

Objectives and aims: The system of the inflammatory 5-lipoxygenase (5-LOX) and its activating protein (FLAP) have been implicated in lipid dysfunction in obesity. We investigated whether this system could participate in the adipogenic action of olanzapine.

Methods: Experiments were performed in 3T3-L1 adipocytes in vitro. Cells were treated with olanzapine and a FLAP inhibitor MK-886. Their lipid content, 5-LOX and FLAP mRNA content, and FLAP protein content were measured.

Results: Olanzapine treatment did not affect the cell content of 5-LOX mRNA; however, it decreased FLAP mRNA content at day five but not 24 hours after olanzapine addition. The inhibitory effect of olanzapine on FLAP expression was confirmed by quantitative Western blot assays. In the absence of a FLAP inhibitor, low concentrations of olanzapine (0.5 and 5 μM) increased lipid content only by about 13% (compared to about a 56% increase induced by 50 μM olanzapine) whereas in the presence of MK-886 these concentrations of olanzapine produced lipid increases comparable to the increase caused by 50 μM. In these experimental conditions, MK-886 alone did not alter the cell content of lipids.

Conclusions: 5-LOX system may be involved in lipid dysfunction not only in conditions of obesity but possibly in SGAD-related metabolic alterations. The known polymorphism in the genes of the human 5-LOX system could play a role in setting a variable individual susceptibility to the metabolic side effects of SGADs.

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