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Acute and chronic effects of drugs that modulate dopaminergic transmission on adipocyte lipolysis and islets insulin secretion.

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Background and Objectives: Metabolic diseases, with glucose intolerance and/or insulin resistance, are related to some drugs which act on the dopaminergic transmission, as the neuroleptics. Our aim was to compare the acute and chronic effects of conventional and atypical antipsychotics on the intermediary metabolism of rodents, by analyzing *In Vitro* the adipose tissue lipolytic activity and the insulin release from pancreatic islets.

Materials and Methods: Wistar rats or NMRI mice were used, and all of them were handled and cared for according to the current European regulation and the Spanish legislation for the care and use of laboratory animals. The effects of haloperidol, risperidone and ziprasidone on metabolic parameters were studied on male healthy animals of 10±2 weeks-old. In the acute analysis those three drugs were tested at 1, 10 or 100 µM in the buffer solution, and for chronic studies they were administered at 2 mg/kg/day orally 8 weeks independently to seven rats on each of the groups. For determining lipolysis, the glycerol release (basal and evoked) was measured from perirenal adipocytes. The insulin secretion was studied with fresh or cultured isolated islets. Results are expressed as mean±s.e.m. and were considered significant if $P<0.05$ after applying the one-way analysis of variance (ANOVA) and the Newman–Keuls test for statistical analysis.

Results: In the acute assays, with haloperidol 100 µM a significant reduction in the basal lipolytic activity was observed. When lipolysis was evoked by isoproterenol 1 µM, the response was similar. Moreover, the insulin secretion diminished significantly after acute incubation of islets at the same concentration of the antipsychotic, and only forskolin 1 µM, which activates the cAMP/protein kinase A (PKA) pathway, reversed partially the haloperidol effect. When the animals were treated chronically with the psychotropic drugs, the adiposity was slightly increased in the risperidone group, although without significance. However, glycerol release by isolated adipocytes was significantly reduced in the risperidone group in comparison with those treated with haloperidol. The lipolytic response induced by isoproterenol or forskolin was similar. Besides, after chronic administration of antipsychotics a small increase in insulin release was obtained in the haloperidol group but the results were not significant when comparing with risperidone treated animals. Interestingly none of the findings described neither in acute experiments nor in chronic ones were reversed by yohimbine, an alpha-2 adrenoceptor antagonist.

Conclusions: Taken together our results suggest that haloperidol might diminish both insulin release and lipolysis when administered acutely by an action on the cAMP/PKA pathway. On the other hand, the reduction of lipolytic activity observed after the chronic administration of risperidone may be related to interruption of free fatty acids release from adipocytes, thus lessening the lipotoxicity on various tissues (liver, muscle, pancreatic ß-cells), which also may explain the lower trend to develop glucose intolerance, metabolic syndrome or diabetes mellitus linked to this drug.

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