

Antipsychotic Drugs And Salivary Leptin Levels In Wistar Rats

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ABSTRACT: Purpose. Mental disorders such as psychosis, agitation, mania, dementia and bipolar disorder are treated with variable doses of antipsychotics. However, these drugs are often associated with metabolic side effects (weight gain), endocrine disruptions, diabetes mellitus and cardiovascular diseases. Unfortunately, a single reliable predictor of weight gain has not been found, but a relation is to be mentioned between the levels of circulating leptin, administration of antipsychotics and weight increase. The aim of this study was to assess the effects of exposure to antipsychotics from both generations on the salivary leptin levels. Material and Methods. Salivary leptin was determined by the ELISA technique, on three groups of male Wistar rats treated with haloperidole, haloperidole decanoate and aripiprazole for 4 weeks. Results. The present study evidences a significant statistical difference between the values of salivary leptin prior to and after the drug treatment with the first generation agents. Aripiprazole produced no changes. Conclusions. The treatment with haloperidole and haloperidole decanoate induces an increase in salivary leptin levels.

KEYWORDS antipsychotics, rats, salivary leptin, weight gain

Introduction

Since the introduction of chlorpromazine in the early 1950s, a large number of antipsychotics (neuroleptics) have been discovered. In recent years the so-called atypical neuroleptic drugs have also become available. [1]. The increasing use of atypical (second generation) antipsychotics has led to a greater appreciation of not only the benefits of these drugs, but also of the spectrum of toxicity that may occur in clinical practice.

Typical drugs still play an important role in the treatment of psychotic disorders and offer a valid alternative to atypicals where atypicals are poorly tolerated. The essential difference between the two groups is the size of the therapeutic index in relation to extrapyramidal side-effects [2-4].

However, most second-generation antipsychotics, and to a lesser degree first-generation antipsychotics, can produce adverse effects (such as substantial drug-induced weight gain) that are a major factor in promoting poor adherence to, and even discontinuation of, antipsychotic treatment on the one hand, and increasing the risk of metabolic syndrome and cardiovascular disease on the other [5-8].

These adverse effects could be explained by a possible impact of antipsychotic drugs on peptide hormonal regulators of metabolic control – leptin, ghrelin and adiponectin.

The purpose of this study was to evidence changes of salivary leptin levels during antipsychotic treatment.

Material and Methods

The study was done according with Directive 2010/63/EU governing animal research in Europe and was approved by The Ethic Committee from The University of Medicine and Pharmacy of Craiova.

21 adult male Wistar rats were divided into three groups of seven (weight 225-240 g, age 70-80 days). For the 28 days period of the experiment, their weight was recorded a jeun, between 9.00 and 10.00 am for an adequate dosing of the substances. All medications were injected.

The animals were administered different drugs, as follows:

- haloperidole (animals labeled from H1 to H7);
- haloperidole decanoate (animals labeled from HD1 to HD7);
- aripiprazole (animals labeled from A1 to A7);

Each animal had a unique record file and they were all kept in normal laboratory conditions.

According to the previously described technique, applied in humans, for collecting the gingival crevicular fluid, as adapted for saliva collecting [9], for 30 sec, saliva was collected on filter paper strips introduced in the oral cavity of the animal. Collecting was done prior to

beginning of drug administration, as well as 24 hours after the last administration. The absorbed liquid was diluted in 100µl phosphate-buffered saline (PBS), the obtained samples being frozen at -20 C until their utilization.

Salivary leptin was determined with the EZRL-83K (Millipore) kit, by the ELISA Sandwich technique for biological assays of rodents, according to the indications of the manufacturer. The results were expressed in ng/ml. Statistical analysis of the obtained results was based on average value±SD (standard deviation) and the Mann-Whitney U-test, the correlations for p<0.05 being considered significant.

Results

Salivary leptin levels prior to the initiation of the treatment ranged between 0,1-0,4 ng/ml (0,20ng/ml for the group treated with haloperidole; 0,21ng/ml for haloperidole decanoate group and 0,15ng/ml for aripiprazole). In the end of the treatment, salivary leptin registered values between 0,2-0,9ng/ml (0,54ng/ml) for the group treated with haloperidole, 0,2-0,6ng/ml (0,38ng/ml) for the one treated with haloperidole decanoate, and 0,1ng/ml -0,2ng/ml for aripiprazole group, respectively. (Table 1)

Table 1. Salivary Leptin levels (ng/ml)

Drug	Salivary leptin before treatment	Salivary leptin after treatment
Haloperidole	0,20±0,11	0,54±0,27
Haloperidole Decanoate	0,21±0,09	0,38±0,14
Aripiprazole	0,15±0,07	0,15±0,05

As to the animal weight, the average value was of 229,85g in the group treated with haloperidole, comparatively with the initial average values of 232,00g; 228,35g, in the group treated with haloperidole decanoate, versus an initial average value of 231,14g, and 230,57ng/ml for aripiprazole group versus the initial average values of 232,71ng/ml. (Table 2)

Table 2. Weight values (g)

Drug	Weight before treatment	Weight after treatment
Haloperidole	232,00±3,95	229,85±3,85
Haloperidole Decanoate	231,14±3,42	228,35±2,57
Aripiprazole	232,71±3,54	230,57±3,65

Discussion

The recognition, management, and if possible, prevention, of major adverse effects of antipsychotics and some other drugs used to treat mental illness is a topic of much debate, because a wide range of side effects may be encountered, especially the metabolic syndrome.

In 2001, Groschl identified salivary leptin in healthy patients and the molecular form in which it is excreted in the saliva [10].

Certain studies have determined the circulating leptin during the administration of antipsychotic drugs, when increased values were observed [11], and other investigations have shown correlations between the values of seric leptin and the weight increase in patients suffering from schizophrenia, subjected to treatments with typical and atypical antipsychotics [12, 13]. Also under study, beside leptin, were other hormones present in the serum (ghrelin, adiponectin, resistin), known as impacting the energetical balance through various mechanisms [14, 15].

Salivary leptin was determined in different pathological situations, sometimes representing a better alternative than determination of the circulating leptin, because the method of leptin collecting and determination in blood (plasma or serum) is quite difficult for the investigator and uncomfortable for the patient, the risk of failure being quite high. But, saliva collecting from both humans and laboratory animals is much simpler, noninvasive, the results obtained being easy to interpret.

The levels of salivary leptin were measured over a 24 hr interval, the circadian rhythm being thus established, a correlation being also stated between the leptin levels from saliva and plasma [16].

The results of the present study, which applied the antipsychotic treatment to rats, evidence a significant statistical difference between the values of salivary leptin prior to and after the drug treatment with neuroleptics, in haloperidole (p=0.032), and haloperidole decanoate groups (p=0.045), but not for the aripiprazole group (p=1.000). As to the differences between the three groups, they are not statistically significant for haloperidole-haloperidole decanoate (p=0.236), only for aripiprazole-haloperidole (p=0.02) and for aripiprazole-haloperidole decanoate (p=0.005).

As for the animals' body weight, the values registered no statistically significant differences for haloperidole group, but significant differences were observed for aripiprazole

($p < 0.05$), and haloperidole decanoate ($p < 0.05$) groups, prior to and after the treatment. Although limited by the duration of the treatment (4 weeks), the literature mentioning an interval of 3-20 weeks of antipsychotic drugs administration necessary for producing modifications in the body weight of human subjects [2], the results support the idea that some antipsychotics modify salivary leptin levels.

Conclusions

The conducted experiment showed that, of the three antipsychotic drugs that we studied, typical (haloperidole and haloperidole decanoate – retard formulation) and atypical (aripiprazole), the salivary leptin levels were modified during the administration of the two neuroleptics belonging to the first generation, higher values being registered.

Determinations of salivary leptin should be continued on larger experimental groups and over longer periods of time, for evidencing the possible body weight modifications in the animals.

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