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Effects of clozapine and haloperidol treatment on plasma concentrations of androgen hormones and androgendependent organ changes in rats

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Abstract

OBJECTIVES: Metabolic and endocrine adverse effects are among the most concerning unfavorable consequences of commonly used psychotropic drugs. The present research was planned to assess and determine the effects of haloperidol and clozapine on testosterone, cortisol, and corticosterone levels and also their influence on androgen-dependent organs in adult male Wistar rats. **MATERIALS AND METHODS:** Animals were casually distributed into three groups (n = 10 in each group). Drugs were administered intraperitoneally for 28 days. The control group received 2 mL of physiological saline, the second group received haloperidol (0.5 mg/kg), and the third group received clozapine (0.5 mg/kg). The subsequent testosterone, cortisol, and corticosterone plasma concentration levels were analyzed with chemiluminescent immunoassay. **RESULTS:** Clozapine and haloperidol treatments altered testosterone hormone levels. Testosterone mean values in both the clozapine (1.00–0.58) and haloperidol (0.65–0.62) groups were found to be lower than compared to controls (P = 0.003, P < 0.001). Histomorphometric analysis results also showed reduced testes size and reduced weight of androgen-dependent organs in drug-treated rats. **CONCLUSION:** It can be suggested that clozapine and haloperidol are effective in reducing the testosterone plasma concentration level and androgen-dependent organ sizes; therefore, clinicians should be aware of these effects when considering the use of antipsychotic drugs.

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Full Text

Introduction

The use and prescription of antipsychotic medications are increasing rapidly worldwide in recent years. Appropriate antipsychotic drug use is largely based on the balance between the risks of the drugs and their benefits.[1] Since the 1950s, antipsychotics have been used for the management and treatment of agitated psychotic illnesses and mental disorders.[2] Antipsychotic drugs can be classified into two major groups: typical (conventional), such as haloperidol and chlorpromazine, and atypical (novel) drugs which are used since the 1990s, such as olanzapine, clozapine, aripiprazole, quetiapine, and risperidone.[3] It is well-known that a large number of psychotropic medications and pharmacological compounds interfere with the endocrine system.[4],[5] Due to the nature of long-term use of antipsychotics, physicians should have appropriate knowledge of their side effects.[6] Antipsychotic-induced metabolic disruptions and endocrine side effects have important clinical implications as they can significantly reduce a patient's quality of life.[7] In recent years, there has been a rising awareness of their sexual, metabolic, and endocrine side effects, and it has become clear that various aspects of sexual function may be adversely affected by antipsychotics.[8] Potential toxic effects from the long-term administration of antipsychotic drugs have been extensively investigated, with the results emphasizing that their side effects and molecular mechanisms must also be taken seriously.[9] Antipsychotic medications are likewise known to influence the hypothalamo–hypophyseal axis.[10] Unfortunately, there is still a substantial gap between the use of psychotropic drugs and the accessible data regarding their safety and efficacy in populations. This has led to a concerted initiative by the pharmaceutical industries and researchers to close this gap.[11] In particular, clozapine and haloperidol are two drugs commonly used in the treatment and management of various psychotic conditions. Clozapine is among the first drugs from the so-called "atypical antipsychotics" class. These agents generate their clinical effects without having parkinsonian side effects similar in magnitude to the classical neuroleptics. Clozapine is generally considered to be one of the most effective antipsychotic drugs to treat bipolar disorder and schizophrenia as well as to provide therapeutic support for other psychoses.[12] Haloperidol is a typical potent neuroleptic drug, a major tranquilizer, and is extensively used in the treatment of delirium, schizophrenia, and alcohol withdrawal, and it is particularly effective in treating the symptoms of psychotic disorders.[13],[14] However, the mechanisms responsible for generating the various adverse antipsychotic-induced endocrine and metabolic side effects are poorly understood. Therefore, to investigate the possible side effects induced by these drugs and elucidate the probable mechanisms involved, we evaluated the results of haloperidol and clozapine use on feeding, weight, androgen-dependent organs, and the levels of cortisol, corticosterone, and testosterone in male rats.

Materials and Methods

Drugs and chemicals

Haloperidol and clozapine were obtained from Sigma Chemicals. Other agents used in this research were obtained from Merck (Sigma-Aldrich) Inc., including lactic acid (2-hydroxypropionic acid), glutaraldehyde (C5H8O2), sodium dihydrogen phosphate (NaH2 PO4.2H2O) caustic soda (NaOH), sodium nitroprusside (Na2[Fe (CN)5 NO]·2H2O), and formaldehyde (HCHO).

Drug preparation

Drug preparation procedures were carried out in accordance with the study by Halim et al.[15] The preparation of a 20 mg/mL solution of haloperidol was performed by dissolving 200 mg haloperidol in 10 mL of lactic acid (1%) with heating to obtain a stock solution. Then, this stock was diluted with distilled water to obtain a solution of 0.5 mg/mL haloperidol, while adjusting the pH to 5.1 with 1N NaOH. Clozapine solutions were prepared daily. One hundred and forty milligram clozapine was dissolved in 0.6 mL 1N HCl with the application of mild heating. This solution was then diluted to obtain the application dose (0.5 mg/mL) of clozapine while also adjusting to 5.1 pH with 1N NaOH.

Animals and drug administration

All applications and experiments were performed according to the most recent versions and amendments of the Guide for the Use and Care of Laboratory Animals.[16] Approval for the experimental procedures used in this study was obtained from the Ethics Committee of Urmia University (Ir. umsu. rec. procedure no. 1390.116). The rats were ordered from the Urmia University Animal Morphology and Physiology laboratory (Wistar, male adults, aged 14–15 weeks, and weighing 270 ± 30 g). Animals were allowed to acclimatize for 1 week before the commencement of the study. Each animal was kept separately in standard filter-top cages inside of ventilated soundproof boxes providing ad libitum feeding and water with 12-h light-dark cycles at a temperature of 22°C and a humidity level of 50%. Any and all precautions that would reduce animal use and the adversities that animals may face were employed to the best of our ability. A total of 30 rats were kept in 15 cages (2 rats per cage) and had ad libitum access to water and food (standard pellet). The total of 30 rats was randomly distributed (10 rats each) into three groups: (1) haloperidol (0.5 mg/kg), (2) clozapine (0.5 mg/kg), and (3) the control group, which was treated with saline (NaCl 0.9%). All

applications were performed daily through intraperitoneal injections for a total of 28 days. The doses given were based on the therapeutic range of these drugs in patients.[17] The total study duration was 50 days. Measurements of weight and food intake were performed every day to track weight loss and to be able to calculate drug dosages of the following day.

Tissue perfusion

When studies were completed, animals were anesthetized and subjected to intracardiac perfusion using sodium nitroprusside (100 mg) and 500 IU heparin in a previously prepared solution of physiologic serum for 5–10 min. Subsequently, 4% of C5H8O2 in a buffer prepared with 0.01 M Na-phosphate at pH = 7.2 was utilized for a second perfusion lasting 15 min. Following fixation, the organs and tissues of interest were then dissected, including the prostate gland, testes, epididymis, and seminal vesicle. All tissues were removed and weighed using a scale with 0.001 g precision (S2202, BEL Engineering).

Histomorphometry analysis of testes

After the testes of the mice were removed, they were fixed in 10% formaldehyde solution for 48 h. Subsequently, paraffin-embedded blocks were prepared by dehydration with graded ethanol series. A rotary microtome was used to cut serial longitudinal sections of 5 μm thickness (Microm, Germany). H and E staining was performed on each section and was evaluated by a Leica DMR microscope (Leica, Microsystems CMS GmbH, Mannheim, Germany).[18] Histological evaluation and measurement of testis diameters were performed on the stained sections.

Food intake and body weight measurement

The food intake and body weight of each rat were measured every day during the 1st week after the beginning of drug treatment. Subsequently, the body weight was recorded two times, at the beginning of the treatment and after 28 days. On the 29th day, the final body weight of each rat was recorded, and scarification was performed. Definite value of 24 h food amount was measured on days 3, 10, 17, and 24.

Statistical analysis

The SPSS software by IBM (version 20) was utilized for performing statistical comparisons and analyses in this study. Quantitative variables were depicted with mean ± standard deviation and range values. The Shapiro–Wilk test and histogram graphs were utilized to evaluate the normality of distributions. Results demonstrated nonnormal distribution of data. The Kruskal–Wallis test was used to compare organ-related changes and hormone levels between the three groups. Subgroup analyses were performed by Dunn's nonparametric post hoc test. Differences in feeding and body weight measured at different time points were assessed by repeated ANOVA analyses followed by post hoc comparisons using the Tukey, Welch, and Fisher's tests, where appropriate. Box plots were used to display differences and trends observed in the comparison of groups. A type 1 error rate of 5% ($P < 0.05$) was set for the determination of significance in all of our comparisons.

Results

On the basis of the measurements taken from the testes in the drug-treated and control groups, the diameters of the testes, compared to the saline-treated group, were significantly reduced in both groups where drug treatments were applied [Figure 1] and [Figure 2]. In regard to histological evaluations, it was clear that the number of blood vessels in the experimental groups had decreased compared to controls. Although the number of Leydig cells decreased in the experimental groups, controls' values were normal. The morphological features of cells in the spermatogenic area of the experimental groups were found to be apoptotic compared to controls.{Figure 1}{Figure 2}

The effect of haloperidol and clozapine on androgen-dependent organs

The data obtained from the weight measurements of androgen-dependent organs of the control and drug-treated rats are given in [Table 1]. A significant difference was detected among the three groups according to the weights of the prostate gland, testes, and epididymis ($P < 0.05$). When the prostate glands of the saline, clozapine, and haloperidol groups were weighed, mean values were found to be 0.58 ± 0.09, 0.47 ± 0.08, and 0.49 ± 0.07 g, respectively. The mean prostate gland weight was measured to be significantly lower among clozapine recipients compared to controls ($P < 0.05$). The mean testes weights of the saline, clozapine, and haloperidol groups were 1.69 ± 0.04, 1.61 ± 0.04, and 1.62 ± 0.03 g, respectively. Compared to controls, the mean weight of the testes in the clozapine and haloperidol groups were significantly lower ($P < 0.05$). In regard to seminal vesicle weight, the saline, clozapine, and haloperidol groups had mean weights of 0.71 ± 0.10, 0.61 ± 0.13, and 0.65 ± 0.07 g, respectively. Similarly, epididymis weight was found to be significantly reduced in the clozapine group 2.54 ± 0.12 (0.34) compared with the saline group (2.67

± 0.10, P < 0.05). Finally, the seminal vesicle weight was similar in all comparisons (P > 0.05).{Table 1}

[Table 2] summarizes the serum hormone and metabolite levels of rats based on the three groups. The only significant difference was determined in the levels of testosterone (P< 0.001), while cortisol and corticosterone concentrations were similar. The mean testosterone levels of the saline, clozapine, and haloperidol groups were 6.04 ± 0.46, 0.94 ± 033, and 0.70 ± 0.34, respectively (P< 0.05). While testosterone levels were significantly higher in the saline group, there was no statistically significant difference between the clozapine and haloperidol groups (P > 0.05). Mean corticosterone levels measured in the saline, clozapine, and haloperidol groups were 116.86 ± 6.15, 117.08 ± 7.06, and 114.06 ± 7.09, respectively. Drug-treated rats and those in the control group exhibited similar serum corticosterone levels [Table 2], P > 0.05]. Finally, mean cortisol levels of the saline, clozapine, and haloperidol groups were as follows: 0.61 ± 0.07, 0.62 ± 0.08, and 0.63 ± 0.07, respectively. Consistent with the previous results, cortisol levels were also found to be close to each other for the control and drug-treated rats.{Table 2}

The influence of haloperidol and clozapine on rats' weight and amount of intake of food

Importantly, there was no significant difference between the initial weights across the rat groups at the beginning of the study (P ≥ 0.05). Repeated variance analyses (ANOVA) showed groups were similar in terms of body weight over the course of the study. However, mean body weight showed anincrease in both drug-treated groups during the 28-day study course compared with the first measurement [Figure 3], F = 956.25, P < 0.001]. The increase was not different in the clozapine and haloperidol groups.{Figure 3}

Furthermore, food intake did not show statistically significant differences among the drug groups (F = 2.36, P > 0.05). However, there was a significant difference in food intake, according to time and time-group interactions. This primarily means that food intake changed with time, and the second outcome is that food intake in different drug groups also differed according to the number of elapsed days (F = 31.95, P < 0.001, and F = 2.52, P < 0.05, respectively). The mean food intake rose for all drug types from day 3 to day 24, but this increase occurred at different time points for different drugs. For instance, the clozapine group reached its highest food consumption on the 24th day, whereas the haloperidol group reached their highest value on the 17th day [Figure 4].{Figure 4}

Discussion

In the current study, antipsychotic drugs (clozapine and haloperidol) were assessed for their effects on serum hormone levels and the features of organs of the reproductive system in male Wistar rats. In an earlier work, de Siqueira et al. assessed olanzapine with varying levels of applied concentration and aimed to determine the effect of these different treatments on the sperm production, testosterone hormone level, and organs of the reproductive system.[19] They found that testes and prostate weight were reduced and plasma testosterone levels were decreased with olanzapine treatments. In addition, they reported testicular degeneration. According to their results, olanzapine (30–35 ng/mL) led to weight loss instead of weight gain. In a study by Choi et al., which assessed clozapine as the antipsychotic drug, it was reportedly found thatfeeding was normal in rats that received clozapine and the overall weight of the same rats were also found to be unchanged with clozapine treatment. On the other hand, olanzapine treatment that was similarly applied to rats in a comparison group was a cause of a significant increase in eating and also the weight of the rats that were female; however, this effect was not observed in male rats.[20] However, these medications are known to cause weight gain in humans. Similarly, Pouzet et al.[21] reported that antipsychotics effects in humans could not be repeated in Wistar rats; thus, Wistar cannot be considered an adequate model for the evaluation of weight gain induced by antipsychotics.

In an earlier study which evaluated the impact of antipsychotics on organ weight, sexual behavior, and hormones, haloperidol and risperidone use were found to decrease serum testosterone levels after 6 weeks of administration.[22] In both haloperidol and risperidone groups, epididymis weight significantly decreased below controls. In addition, in the 6th week, the weights of other reproductive system organs (epididymis, vesicle, and prostate) were found to be significantly decreased in only those that had received haloperidol. Haloperidol has been shown to cause problems in sexual function and reproductive organs in various studies.[19],[22],[23],[24],[25] The effects of antipsychotics on sexual function have been attributed to the blockade of dopamine receptors.[24] They were also reported to cause a loss of ovarian function and secondary amenorrhea in women, as well as lower testosterone level in men. However, there are also studies suggesting that antipsychotic drugs do not have any significant effect on plasma hormone levels such as cortisol, corticosterone, or testosterone.[3],[26],[27] Several authors have associated this testosterone decrease with an antipsychotic-induced hyperprolactinemia, and higher body mass index and insulin levels have been shown to be the most important factors associated with lower serum testosterone levels.[28] With regard to weight gain and food intake, several studies confirm our findings.[3],[20],[21] For instance, Lin et al.[3] found that haloperidol treatment did not influence weight and/or feeding in murine models.[3] It was also shown that a 4-week haloperidol treatment led to higher serum insulin levels, whereas risperidone treatment led to high glucagon, less feeding, and lower weight. In humans, clozapine is the drug most likely to cause weight increase.

However, some studies have shown that it did not cause similar effects in murine models.[20] In addition, in most clozapine studies, rats did not demonstrate any changes in their weight and also the amount of feeding. However, the absence of these effects may be explained by the fact that the serum drug concentration does not reach the therapeutic cutoff point in human blood. In our study, in which the dose of 0.5 mg/kg/day for each drug was administered, significant differences were observed between the drug and control groups in terms of androgen-dependent organ weights. According to these results, weights of the prostate glandtestes, and epididymis showed a significant decrease in the drug groups, especially in the clozapine group. According to the results of the pairwise comparisons, both the clozapine and haloperidol groups had significant differences only in terms of testicular weight. These differences could be detected even though we administered only a low dose for 28 days. According to the serum hormone levels, the testosterone level showed a significant decrease in both drug groups, but the cortisol and corticosterone levels did not change significantly among the groups. This result confirms some of the findings in the literature.[25],[26] Similarly, the last bodyweight measurement did not show a significant change with respect to the drug groups or drug and time interactions. A comparison of the mean bodyweight of the rats before and after treatment showed that both the drug-treated and control rats manifested the same increase in body weight. Therefore, we can conclude that a slight increase in rats' weight is time-dependent, and feeding changes are also caused by time and drug group interaction. The amount of food intake decreased most in haloperidol, but this is a time-bound effect of the drug.

The assessment of hormonal, endocrine, and metabolic side-effects caused by antipsychotic drugs in murine models can increase our understanding of these widely used drugs and can contribute to the creation of better treatment approaches. The adverse effects of antipsychotics on the endocrine system are a particular feature that must be meticulously considered when deciding on treatment approach and medication dosage. In addition to often-encountered side effects, the results of this study show that patients receiving antipsychotics should be screened for thyroid dysfunction and possible abnormalities in fertility associated hormones. It is apparent that further studies are required to elucidate these effects.

Despite useful therapeutic options provided by antipsychotic drugs, there are adverse effects associated with the length and dosage of these medications that may affect the endocrine system in various ways. We conclude that based on the current evidence, antipsychotic medications can cause alterations in the morphology and function of reproductive system organs in males that may cause infertility. Clozapine and haloperidol administration has been shown to cause testicular degeneration and reductions in the weights of the epididymis, testes, and the prostate gland, as well as testosterone decrease. This study also showed that the observed effect on weight gain in rats was incompatible with human evidence, and in this context, the theory that mice could not be a model for the increase in weight gain associated with antipsychotics in humans is supported. Moreover, the fact that the increase in weight does not depend on the drugs but on time, and there is no effect of the drugs on the amount of food intake while having different effects over time, is a striking result. It is important that clinicians recognize the effects of drugs on laboratory interpretation and avoid a wrong diagnosis and unnecessary treatment. Above all, due to the limited knowledge in published studies regarding the endocrine influences of psychoactive drugs; further studies, preferably with different species, are required.

Conclusion

It can be suggested that clozapine and haloperidol are effective in reducing the testosterone plasma concentration level and androgendependent organ sizes; therefore, clinicians should be aware of these effects when considering the use of antipsychotic drugs.

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Conflicts of interest

There are no conflicts of interest.

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