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Research Article

Haloperidol for modelling osteoporosis in rats

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Abstract

Introduction: Various experimental models of osteoporosis are well-known and presented in the literature, yet we did not find a description in the available literature of the possibility of using antipsychotics to induce osteoporosis in rats. **The aim of the study:** We aimed to develop a "haloperidol model" of osteoporosis and to evaluate its efficiency in rats.

Materials and Methods: Wistar rats were divided into 2 groups (20 animals each): control (saline) and experimental (haloperidol). Haloperidol was administered intraperitoneally for 90 days according to the regimen from 15 mg/kg/day to 5 mg/kg/day as 1 mL per 100 mg of rat body weight of saline solutions in corresponding concentrations. We performed blood tests for total calcium, alkaline phosphatase, and urine tests for oxyproline to demonstrate that bone metabolism changes in rats were consistent with osteoporosis. After 90 days, we finalized the experiment and performed a histomorphometry assessment of the bone tissue of rats' vertebrae (the average diameter of the spongy trabecula, the thickness of the cortical plate and the area of the intertrabecular space were evaluated) and microelement analysis (Ca, Sr, Zn, Cu).

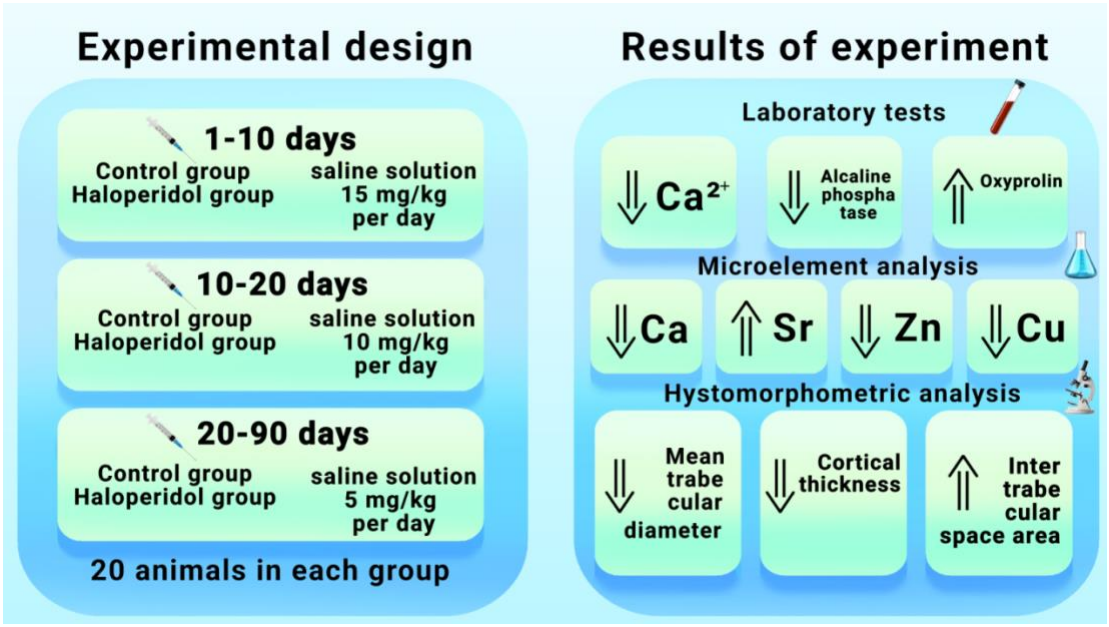
Results: We found that haloperidol induced a decrease in the level of total calcium by 2.2 times and alkaline phosphatase by 1.6 times in the blood, an increase in oxyproline in the urine by 1.7 times; a reduction in the average diameter of trabeculae by 2.2 times and the thickness of the cortical layer by 2 times, an increase in the area of the intertrabecular space by 2 times; a deficiency in the content of Ca, Zn and Cu, and an increase in the content of Sr, as compared with such in the control group.

Conclusion: Prolonged administration of haloperidol to rats intraperitoneally for 90 days according to the regimen from 15 mg/kg/day to 5 mg/kg/day causes the bone metabolism changes with all characteristics of bone destruction, detected by biochemical, histomorphometry and microelement analyses of bone tissue and blood. Haloperidol could be used to model experimental osteoporosis and the "haloperidol model" could be used to study potential of new antiresorptive agents.

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Graphical Abstract



Keywords
antipsychotics, haloperidol, experimental osteoporosis, experimental rats

Introduction

Currently, the most commonly used model for experimental reproduction of systemic osteoporosis is oophorectomy with median laparotomy in estrogen-deficient female rats. This model is suitable for studying the pathogenesis of postmenopausal osteoporosis and methods of its drug therapy (Matsumoto et al. 2006). Experimental models of osteoporosis in male rats during ovarian gland removal (orchidectomy) are also used to model androgen deficiency and subsequent loss of bone density (Blouin et al. 2008; Inada et al. 2011).

Experimental models of osteoporosis associated with long-term, low-calcium diet are well-established. So in the model by Gala et al. (2001), feeding rats a low-calcium (less than 0.3%) diet for two months resulted in significant reductions in bone mineral density and bone strength (Omi and Ezawa 2011). At the same time, the best result was achieved by combining two experimental models: ovariectomy in rats and animal management on a low-calcium diet. When two models of experimental osteoporosis were combined, signs of decreased bone density occurred earlier and were accompanied by changes even in flat skeletal bones (Teófilo et al. 2003).

One known model of experimental osteoporosis is steroid-induced osteoporosis (Huo et al. 2022). Prednisolone acetate was administered to rats at doses of 1.5, 3.0 and 6.0 mg/kg per day orally, with significant cortical bone loss and serum resorption markers (Huo et al. 2022). In studies by Ziganshina et al. (2000), prednisolone pulse therapy in rats at a therapeutic dose for 2 weeks resulted in increased urinary oxyproline, decreased alkaline phosphatase, and decreased total blood calcium levels (Ziganshina et al. 2000).

Alternative experimental models of osteoporosis in rats are also found in the literature, as in Sananta et al. (2026), who describes an experimental model using leuprorelin acetate, a gonadotropin-releasing hormone agonist, in combination with a low calcium diet and immobilization of experimental animals. Significantly increased levels of tartrate-resistant acid phosphatase and N-terminal procollagen type 1 propeptide (PINP) were recorded in rat bone tissue (Sananta et al. 2026).

At the same time, the osteoporetic effect of neuroleptics on bone tissue, due to the prolactin-increasing effect of most typical neuroleptics, is actively discussed in the literature (De Hert et al. 2016; Di Filippo et al. 2020). But in the literature available to us, we have not identified

experimental animal models of osteoporosis using antipsychotics and the detection of osteoporetic effects with long-term use of haloperidol. Haloperidol has been often used in experimental models to study motor disorders arising from neuroleptic treatment (Andreassen and Jørgensen 1995). Extrapyramidal side effects and its ability to induce catalepsy were identified in the experiment, with haloperidol doses of 0.3 mg/kg and 0.1 mg/kg causing decreased locomotor activity but no cataleptogenic state (Drinkenbur et al. 1999). Moreover, in the studies by Bricker (2014), the occurrence of catalepsy in rats following the administration of haloperidol at a dose of 0.29-0.31 mg/kg body weight was detected using an original technique (Bricker et al. 2014). Most of the experiments with haloperidol focused on to the analysis of subcortical brain structures and the functioning of the neurotransmitter system (Bressan et al. 2024). The study by Nikolić et al. (2017), which evaluated the bone condition of rats prenatally administered haloperidol, found a negative effect of haloperidol administration on rat bone tissue (Nikolić et al. 2017). In this regard, **the aim of the study** was to develop and evaluate the effectiveness of the haloperidol osteoporosis model in an experiment on experimental rats.

Material and Methods

Animals

A 90-day experiment was conducted on Wistar rats, 20 animals in each group. The age of the animals was 3.2 ± 0.8 months, the sex ratio was close to 1:1. The study was approved and authorized by the Ethics Committee of the Kazan State Medical Academy of the Ministry of Health of the Russian Federation (Minutes No. 4/05 of June 6, 2013).

Animal groups

The animals participating in the experiment were randomly divided into 2 groups of 20 animals in each group (n=40):
1 – control group
2 – test group (haloperidol injection)

Drug under study

Haloperidol was administered intraperitoneally on days 1-10 at a dose of 15 mg/kg per day (1 mL of 0.15% haloperidol solution per 100 grams of rat body weight), on days 10 to 20 – at a dose of 10 mg/kg per day (1 mL of 0.1% solution per 100 grams of weight) and from days 20 to 90 – at a dose of 5 mg/kg per day (1 mL of 0.05% solution per 100 grams of weight). A 0.5% haloperidol solution (using Hedeon Richter haloperidol as a 0.5% solution in 1 mL ampoules) was diluted with physiological saline and administered as 1 mL of drug solution per 100 mg of rat weight.

High doses of the antipsychotic (15 mg/kg per day in rats) were used to mimic administration of extra-high doses of the drug in psychiatric patients, which are used in practice to relieve acute psychosis on the first day of hospitalization with adjustment of human doses to rodents, rats (REFERENCES - 2). The dose of haloperidol was then reduced to maintenance dose of 5 mg/kg per day (Ziganshina et al. 2011), which was nicely tolerated by rats.

To convert the dose of haloperidol from humans to rats, the interspecies dose conversion factor (depending on body surface area) was used, which for the rat is 6.2 (FDA 2005; Shekunova et al. 2020).

Study design

Blood was collected from the tail vein to determine total plasma calcium by O-cresolphthalein colorimetry and serum alkaline phosphatase activity. For the determination of oxyproline in urine (by kinetic colorimetry according to the method of Bergmann and Loxley (1963), rats were moved to metabolic cages for three days for collecting daily urine.

Rats were removed from the experiment by decapitation under ether anesthesia in accordance with International Standards (Council of the European Communities Directive 2010/63/EU). The isolated vertebrae of animals were dissected free from soft tissues and subjected to a microelement study for the content of trace elements (Ca, Sr, Zn, Cu) in bone tissue by atomic absorption spectrophotometry using a SA10 MP device (Kazan Optical and Mechanical Plant, Russia) in the laboratory of the Academy of Sciences of the Republic of Tatarstan (Russia). The isolated vertebrae of the animals were then subjected to histomorphometric analysis in the pathology department of the Republican Clinical Hospital. The average diameter of the bone trabeculae and the thickness of the cortical layer of the vertebrae were determined (American Society for Bone and Mineral Research 1987). The area of the intertrabecular space was

determined by a proprietary automated image analysis method applied to digital images of histological sections via PhotoM-1.21 software.

Statistical data processing

Statistical analysis of the results obtained was carried out using SPSS 14.0 software for Windows (SPSS Inc., Chicago, IL, USA) (2016); the sample distributions were compared with a normal distribution using the Kolmogorov-Smirnov test. In the normal distribution of values in the study groups, the following parameters were calculated: mean – M and standard deviation (M±SD) or the standard error of the mean. Differences between groups were evaluated using Student's t-test or the Student-Newman-Keuls post-hoc test. The results were considered significant at $p < 0.05$.

Results

Analysis of the obtained study results indicates a significant disbalance in the content of biochemical markers of bone metabolism in rats with prolonged administration of antipsychotic. Haloperidol administration showed a 2.2-fold decrease in blood calcium levels compared to such in the control group rats (Fig. 1A).

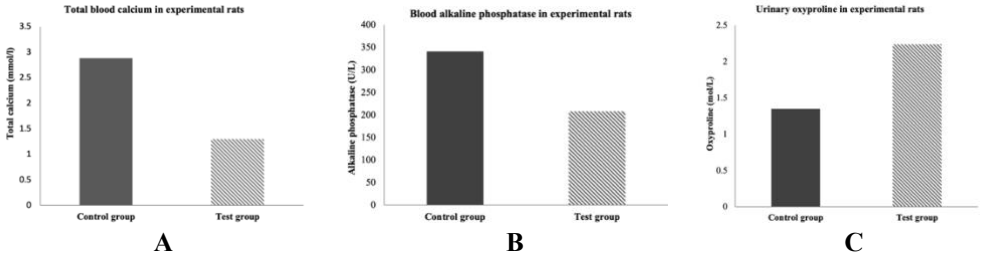


Figure 1. Results of biochemical parameters of bone metabolism in groups of animals following the administration of haloperidol and in control groups after the experiment: **A** – blood total calcium in test and control animals ($p = 0.00816$); **B** – blood alkaline phosphatase in test and control animals ($p = 0.0341$); **C** – urinary oxyproline in test and control animals ($p = 0.0209$).

At the same time, a 1.6-fold decrease in the level of alkaline phosphatase in rats was observed following the administration of haloperidol, which may indicate a disturbance in the process of bone formation (Fig. 1B).

During the reduction in calcium and alkaline phosphatase in the blood of test animals, a 1.7-time increase in the content of oxyproline in urine was observed compared to such in the control group (Fig. 1C). Oxyproline is the degradation product of type 1 collagen most present in bone tissue. An increase in its content may indicate a process of bone destruction with prolonged administration of haloperidol.

Analysis of the microelement composition of the bone tissue of the vertebrae of animals revealed a significant disbalance in the content of macro- and microelements in rats following the administration of haloperidol (Table 1). Bone calcium was 1.7-fold lower in rats when haloperidol was administered compared to such in control. It is possible that the pronounced sedative effect of haloperidol led to hypodynamia and a decrease in the appetite of experimental animals.

Table 1. Indicators of macro- and microelements of rat vertebral bone tissue during haloperidol administration and in the reference group (M ± SD)

Groups of rats	Indicators of macro- and microelements			
	Ca (mg)	Sr (mcg)	Zn (mcg)	Cu (mcg)
Control	8622.28±377.69	5.48±0.58	59.62±5.38	21.12±3.82
Test	5083.42±257.36	8.75±0.72	38.18±3.63	10.74±3.15
P	0.00813	0.0352	0.0255	0.0126

After 3 weeks of the experiment, when the daily dose of haloperidol was 15 mg/kg, the weight of the animals decreased by an average of 18.6%. In rats at this high dose of antipsychotic, signs

of catatonia were detected, and 5 animals died. But a reduction in the dose of antipsychotics led to recovery of body weight in rats and by the end of the experiment the animals gained, on average, more than 12.6% of their original weight. The revealed decrease in the calcium content in the blood and in the bones may indicate inhibition of the process of synthesis of bone tissue, as well as a disbalance of its absorption in the intestine. Under the influence of haloperidol, the process of bone remodeling shifted towards its resorption.

The content of strontium in bone tissue in rats significantly increased (1.6 times compared to such in the control group). The accumulation of strontium in animal bones can be explained by the competitive substitution of calcium ions for strontium ions in the hydroxyapatite crystal. Perhaps, under the influence of the osteoporotic effect of haloperidol, calcium was displaced from bone structures, which is confirmed by its deficiency in experimental animals. The experiment also revealed a decrease in the content of zinc and copper in the bone tissue of rats – 1.6 and 1.9 times, respectively (Table 1). Zinc and copper are major coenzymes in the bone synthesis process. Zinc is involved in the activation of osteoblast function, so its low content may indicate the predominance of the resorption process in the bones of rats. Copper deficiency leads to the synthesis of defective collagen and inhibits the formation of mature bone tissue.

Our assumptions were confirmed in the analysis of histomorphometry data of the vertebrae of experimental animals (Table 2). Significant destruction of bone tissue with all signs of osteoporosis was revealed. Haloperidol administration showed a significant decrease in the average diameter of the vertebral spongiform trabeculae by 2.2 times compared to such in the control group rats.

The thickness of the cortical plate of the vertebrae also significantly decreased by 2 times compared to such in the control (Table 2). The cortical bone is a rather dense tissue composed of a compact bone, with a relatively low metabolic rate; therefore, such a rapid decrease in the thickness of the cortical layer indicates a significant resorptive effect of haloperidol.

Due to a decrease in the thickness of the cancellous trabeculae, there was a 2-fold increase in the area of the marrowspace area compared to such in the control group (Table 2).

Table 2. Histomorphometric evaluation of rat vertebral bone in haloperidol (test) group and in the reference group (M ± SD)

Groups of rats	Histomorphometric evaluation of rat vertebral bone		
	Mean trabecular thickness (μm)	Cortical thickness (μm)	Marrowspace area (%)
Control	58.26±3.53	77.91±3.28	19.28±1.34
Test	26.92±4.55	38.73±2.08	38.62±1.76
P	0.00724	0.00614	0.00325

An increase in the porosity of bone tissue, which means a decrease in its density, indicates the development of osteoporosis, the predominance of resorption processes over bone formation (Figs 2, 3).

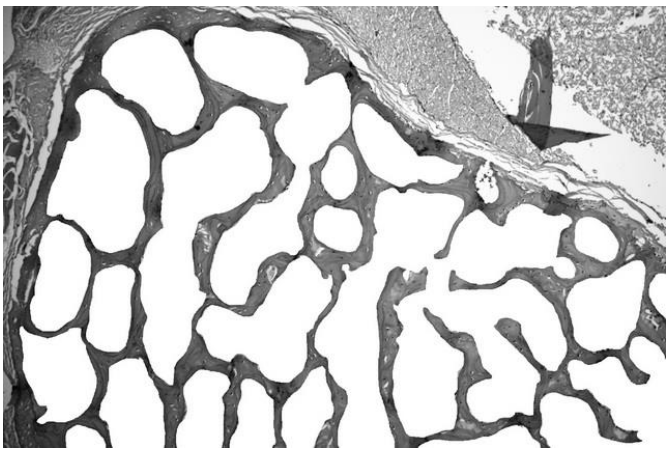


Figure 2. Histological section of bone tissue of the control rats (saline) (× 200).

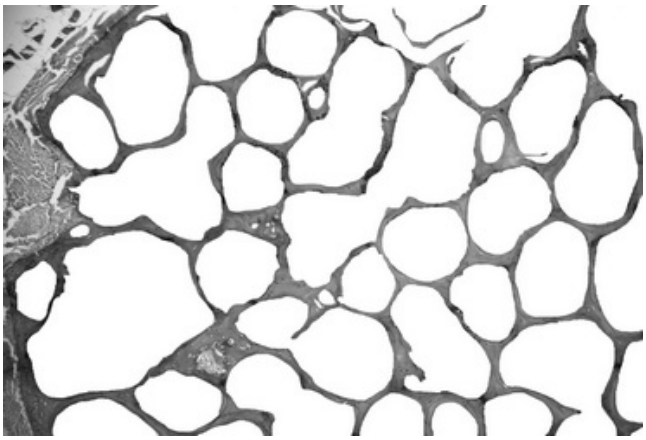


Figure 3. Histological section of the bone tissue of the haloperidol treated rats (× 200).

Discussion

The literature discusses the role of neuroleptics in the process of bone destruction and the development of their side effects with an increase in prolactin levels, which reduces insulin sensitivity or indirectly reduces androgen and estrogen levels (Lin et al. 2014). Sex hormones are actively involved in bone metabolism; estrogen receptors are found on the surface of all major types of bone cells – osteoclasts, osteoblasts, and osteocytes (Chen et al. 2021). Estrogens prevent bone resorption by inhibiting osteoclast activity and are associated with inhibition of the synthesis of IL-1 interleukins, IL-6, tumor necrosis factor, and several others that are involved in bone resorption (Siafis et al. 2023). Neuroleptics from different chemical classes exert various effect on prolactin levels. According to most studies, typical antipsychotic – specifically, butyrophenone derivatives (haloperidol) and thioxanthenes (flupentixol) (Kudo and Ishizaki 1999; McGrane et al. 2022) and the atypical antipsychotic risperidone (Huang et al. 2011; Al Jumaili and Jain 2022) – are associated with a higher frequency of side effects) and, although there are opinions that their side effects are associated with more frequent prescription of prolonged and intramuscular forms of drug administration (Berezancev 2020; Lin et al. 2025). Haloperidol continues to be often used in psychiatric hospitals in Russia, due to its effectiveness in the treatment of various forms of schizophrenia, the low cost of the drug and the presence of various forms of the drug on the market (Miroshnichenko 2023). The data of our experimental study allow us to conclude that the drug has a negative effect on the state of bone tissue in experimental animals (Ilyina 2024). During 90 days of the experiment, vivarium animals underwent all changes in bone tissue characteristic of systemic osteoporosis, confirmed by data from biochemical, microelement and histomorphometric analyses.

The experimental model of osteoporosis we proposed is reproducible in laboratory conditions and can be used to study the pharmacological effects of antipsychotics with drugs of other groups on bone tissue when used together. The use of drugs for the treatment of osteoporosis in patients of a psychiatric clinic is currently limited, due to the low study of this issue. The use of our model of experimental osteoporosis will allow investigating the safety and efficacy of therapy with antiresorptive drugs in this category of patients.

Analysis of the literature allows us to conclude that there are no similar models of experimental osteoporosis based on prolonged administration of haloperidol to rats.

Our study results indicate the need for detailed monitoring of patients taking haloperidol for a long time due to the risk of bone loss development. Even the administration of maintenance therapeutic doses of the drug for a long time can lead to a negative effect on the bone tissue of the patient. Currently, there are no randomized studies on the risks of osteoporosis development in patients taking other drugs with antipsychotics that also disrupt bone metabolism. Due to the duration of antipsychotic therapy, which is often lifelong, with a high prevalence of polypharmacy among these patients and the presence of concomitant pathology, the assessment of undesirable drug effects is significantly complicated. Our proposed model of "haloperidol osteoporosis" will allow conducting research in this direction and, in the future, will help reduce the risks of osteoporosis development in patients of psychiatric hospitals.

Conclusion

Prolonged administration of haloperidol to rats according to the intraperitoneal scheme (1-10 days – 15 mg/kg per day, 10-20 days – 10 mg/kg per day and 20-90 days – 5 mg/kg per day) causes the bone metabolism and structure changes with all characteristics of bone loss, detected by biochemical, histomorphometry and microelement analyses of bone tissue and blood. Haloperidol could be used to model experimental osteoporosis and the "haloperidol model" could be used to study potential new antiresorptive agents.

Additional Information

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics statement

The study was approved and authorized by the Ethics Committee of the Kazan State Medical Academy of the Ministry of Health of Russia (Minutes No. 4/05 of June 5, 2013).

Acknowledgement

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Data availability

All of the data that support the findings of this study are available in the main text.

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Author Contributions

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