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Short Communication

Regulation of 11β-hydroxysteroid dehydrogenase isoforms – novel drug targets for osteoporosis therapy

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Abstract

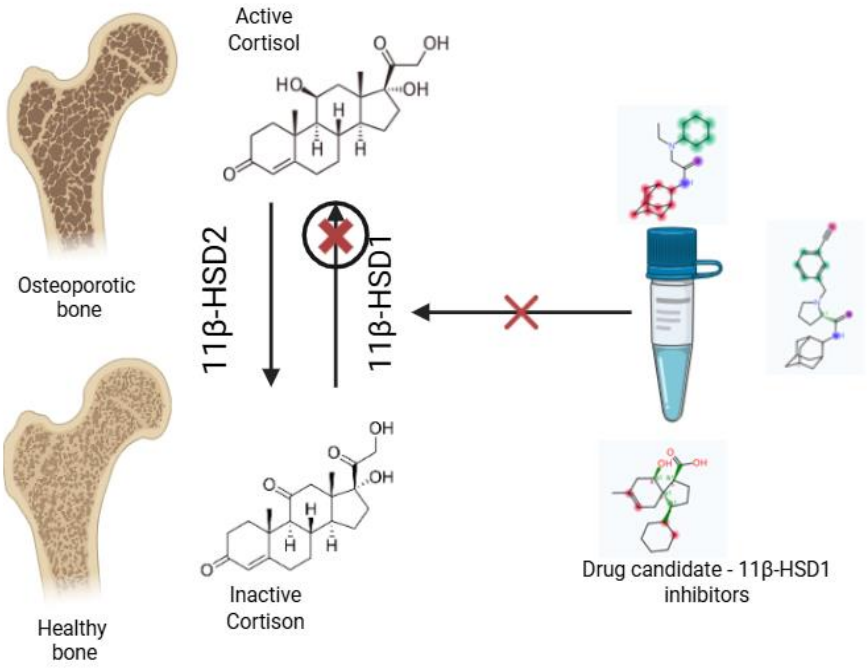
Introduction: Osteoporosis is an significant medical and social public health problem in an aging or elderly society, the issue of pharmacological correction of which remains unresolved to this day.

Materials and Methods: The rationale for this idea stems from our previous findings on the role of 11B-HSD type 2 in bone remodeling and osteoreparation, combined with a content analysis and literature review of scientific publications from PubMed, Scopus, Cyberleninka, Google Scholar, and ResearchGate.

Results and Discussion: Current understanding of the molecular mechanisms of bone homeostasis allows for a significant shift and expansion in the paradigms for treating and preventing osteoporosis. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is a key metabolic enzyme that catalyzes the intracellular conversion of inactive glucocorticoids into physiologically active ones. Research conducted over the past decade has shown that abnormal 11β-HSD1 activity contributes to the pathogenesis of obesity, type 2 diabetes, metabolic syndrome, and osteoporosis. The scientific challenge of regulating the activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) isoforms and restoring homeostasis in the 11β-HSD1/11β-HSD2 enzymatic system is proposed to be addressed through the design and application of novel azole-based heterocyclic compounds as 11β-HSD1 inhibitors.

Conclusion: The development of azole-based heterocyclic 11β-HSD1 inhibitors is expected to yield promising drug candidates for pharmacologically correcting impaired bone remodeling and repair.

Graphical Abstract



Keywords

osteoporosis; 11β-hydroxysteroid dehydrogenase; regulation; 11β-HSD inhibitors; drug targets

Introduction

The skeleton represents one of the classical targets of glucocorticoid hormones. Corticosteroid activation in conditions such as hypercortisolism, long-term glucocorticoid therapy, or aldosteronism has been consistently associated with a reduction in bone mineral density (Frenkel et al. 2015; Kuipers et al. 2015). Recent advances have further underscored the critical role of steroid hormone metabolism in bone development and differentiation. Notably, the group led by Hao Xiao demonstrated that reduced expression of 11β-HSD2 predisposes to osteoporosis induced by prenatal caffeine exposure in male rats (Xiao et al. 2020). In parallel, a team of American researchers identified Hsd11b1 as a pharmacological target of a novel compound capable of limiting osteogenesis and restraining osteoclast functional activity (Garcia et al. 2021).

Building on these findings, the present study aims to establish a scientific rationale for targeting the regulation of 11β-hydroxysteroid dehydrogenase (11β-HSD) isoforms and restoring homeostasis within the 11β-HSD1/11β-HSD2 enzymatic system. The research team proposes the development and application of novel 11β-HSD1 inhibitors as a foundation for innovative pharmacological strategies designed to correct disturbances in bone remodeling and osteorepair.

Materials and Methods

The rationale for this idea stems from our previous findings on the role of 11B-HSD type 2 in bone remodeling and osteoreparation, combined with a content analysis and literature review of scientific publications from PubMed, Scopus, Cyberleninka, Google Scholar, and ResearchGate.
This study was supported by the Russian Science Foundation, grant No. 25-14-00244, https://rscf.ru/project/25-14-00244/.

Results and Discussion

Previously, the authors of this study demonstrated that mice with the Hsd2$^{-/-}$ genotype, characterized by the absence of 11β-HSD2 expression, exhibit a statistically significant decrease in bone mineral density (BMD) by the age of six months, which further progresses at seven and eight months of life. By the eighth month, the reduction in BMD is accompanied by a statistically significant decline in bone microcirculation and an increase in the endothelial dysfunction index, indicating the involvement of endothelial dysfunction and impaired nitric oxide metabolism in the pathological process. These findings are consistent with previously reported vascular endothelial alterations observed in rats with osteoporosis following bilateral ovariectomy (Sobolev et al. 2018; Korokin et al. 2022).

Considering the interplay between endothelial dysfunction, atherogenesis, and bone remodeling disorders, in the present study we also evaluated bone tissue in double transgenic mice with the Hsd2$^{-/-}$/Apoe$^{-/-}$genotype, lacking expression of both 11β-HSD2 and apolipoprotein E. Previous studies have shown that such mice exhibit a pronounced enhancement of pro-inflammatory processes in the vascular endothelium. Based on the experimental evidence, it is clear that cortisol metabolism represents a key regulatory factor in bone tissue trophism, metabolism, and mineralization, while elevated cortisol concentrations trigger a cascade of processes ultimately leading to impaired bone trophism and osteoporosis (Korokin et al. 2022).

In a femoral fracture model, dysregulation of steroid hormone metabolism in animals with the Hsd2$^{-/-}$ and Hsd2$^{-/-}$/ApoE$^{-/-}$ genotypes was shown to increase the incidence of nonunion fractures by 3- and 3.5-fold, respectively, compared with wild-type animals. These findings confirm that in the absence of 11β-HSD2 expression, bone resorption processes driven by osteoclast differentiation surpass osteosynthesis. The previously obtained results were corroborated in the present study: in experimental groups, six weeks after modeling proximal femoral metaphysis fractures (at an overall age of 7.5 months), a decrease in bone mineral density was observed, which was more pronounced in mice lacking expression of both 11β-HSD2 and ApoE (Korokin et al. 2023).

At the same time, experimental evidence has emerged indicating that 11β-HSD1 is an attractive pharmacotherapeutic target for the treatment of diseases associated with impaired steroid hormone metabolism. To date, 25 drugs based on 11β-HSD1 inhibitors are at different stages of development, including 8 in various phases of clinical trials and 18 at the preclinical stage. 11β-HSD type 1, the predominant reductase in most intact cells, catalyzes the regeneration of active glucocorticoids, thereby enhancing glucocorticoid action at the cellular level. The expression of 11β-HSD1 is selectively increased in adipose tissue during obesity, where it contributes to metabolic complications. Similarly, 11β-HSD1 levels are elevated in the aging brain, exacerbating glucocorticoid-associated cognitive impairment. Deficiency or selective inhibition of 11β-HSD1 has been shown to improve multiple parameters of metabolic syndrome in experimental animal models and in human clinical trials, as well as to enhance cognitive function (Chapman et al. 2013; Kupczyk et al. 2022).

Over the past decades, various inhibitors of 11β-HSD1 have been identified. Most of these inhibitors have been discovered through high-throughput screening and structure-based molecular design strategies. According to structure–activity relationship (SAR) studies, the adamantyl group is one of the most frequently occurring structural motifs, present in compounds such as AZD-8329, the “KR” series, UI-1499, and PF-877423. This fragment forms hydrophobic interactions with surrounding residues, including Tyr158, Ala198, Ile155, Leu192, and Ala201, and demonstrates the ability to interact with the lipophilic scaffold of 11β-HSD1, thereby increasing compound activity duration. However, evidence suggests that the adamantyl group may also contribute to metabolic disturbances, leading to adverse effects (Zhu et al. 2008).

To overcome this limitation, additional hydrophilic groups – such as amide, carboxylic acid, or hydroxyl groups – are often introduced to optimize the physicochemical properties of these compounds. Moreover, similar to the adamantyl fragment, hydrophobic substituents such as phenyl or cyclohexyl groups are also commonly found in 11β-HSD1 inhibitors, where they establish hydrophobic interactions with the enzyme (Zhu et al. 2008).

Since most 11β-HSD1 inhibition experiments have been carried out using different experimental approaches, reported IC50 values vary, making it difficult to directly compare inhibitory activities across compounds. In general, inhibitors capable of forming a greater number of hydrogen bonds tend to exhibit stronger inhibitory activity. For example, KR-67183 interacts with human 11β-HSD1 through hydrogen bonds with Ser170 and Leu217, similar to KR-67105. However, KR-67183 demonstrates approximately twenty-fold greater inhibitory potency than KR-67105, which can be attributed to its additional interactions with Val227 and Leu230 residues.

In the study by Ji Seon Park and colleagues (Park et al. 2014), the antidiabetic, anti-adipogenic, and anti-osteoporotic activities of KR-67500 were investigated as a novel selective 11β-HSD1 inhibitor. KR-67500 was shown to improve glucose tolerance in vivo and enhance insulin sensitivity in DIO-C57BL/6 mice. The compound inhibited cortisone-induced differentiation of 3T3-L1 cells into adipocytes, promoted BMP2-induced osteoblastogenesis in C2C12 cells, and suppressed RANKL-induced osteoclastogenesis in bone marrow-derived macrophages. These findings suggest that KR-67500, as a selective 11β-HSD1 inhibitor, may provide a novel therapeutic window for the prevention and/or treatment of type 2 diabetes, obesity, and osteoporosis.

Overall, a review of the available literature demonstrates that, despite considerable research efforts, only seven selective 11β-HSD1 inhibitors have advanced from basic research into clinical testing (phase I–II) for indications related to metabolic syndrome, type 2 diabetes, and obesity. For instance, INCB13739 and RO-151 were evaluated in patients with type 2 diabetes (Heise et al. 2014). MK-0916 was studied in patients with type 2 diabetes and metabolic syndrome, while MK-0736 was investigated for the treatment of comorbid obesity and hypertension (Wright et al. 2013; Shah et al. 2011), although its development was subsequently discontinued. None of these inhibitors demonstrated significant improvements in overall clinical outcomes, with the exception of INCB13739, which successfully reduced HbA1c and fasting plasma glucose levels in patients with type 2 diabetes. Nevertheless, this compound was not brought to market for reasons that remain unclear (Rosenstock et al. 2013). To date, no phase III clinical trials of 11β-HSD1 inhibitors have been reported. Current knowledge on these inhibitors is based entirely on phase 0 and phase II clinical trial results. Thus, no 11β-HSD1 inhibitor has been approved to date.

In 2022, a research team from the United Kingdom, led by Nantia Othonos, completed an experimental, randomized, double-blind, placebo-controlled study of the drug AZD4017 at the Churchill Hospital research unit in Oxford, UK (NCT03111810). A total of 32 healthy male volunteers were randomized to receive either AZD4017 (an 11β-HSD1 inhibitor) or placebo alongside prednisolone treatment. The investigational drug was administered to prevent the adverse effects of glucocorticoids without impairing their primary therapeutic action. Although the primary endpoint of the study (changes in glucose levels during a two-step hyperinsulinemic–euglycemic clamp) was not achieved, hepatic insulin sensitivity worsened in the placebo group but not in the AZD4017 group. Moreover, pharmacological modulation of lipid metabolism and improvements in bone regeneration were observed with AZD4017. The compound demonstrated a positive therapeutic effect on lipid metabolism markers as well as bone tissue repair. Nighttime blood pressure was higher in the placebo group compared with the AZD4017 group. The researchers reported four adverse events associated with AZD4017 administration, none of which were classified as serious (Othonos et al. 2023).

Conclusion

Thus, the regulation of 11β-HSD homeostasis sheds light on the emerging biology of intracrine control of steroid hormones. Modulation of this homeostasis offers new therapeutic opportunities for the treatment of a wide range of diseases associated with impaired steroid hormone metabolism. Within the framework of the present study, the research team has developed a series of 11β-HSD1 inhibitors and is investigating the potential for regulating homeostasis within the 11β-HSD1/11β-HSD2 system to establish novel therapeutic strategies for the correction of bone remodeling and osteorepair processes.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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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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