ChatGPT

Summary of PubMed Studies about CNX-013-B2 (Rexinoid)

Background

Retinoid X receptors (RXRs) are nuclear receptors that modulate gene expression in metabolic tissues and have emerged as therapeutic targets for insulin resistance, dyslipidemia and obesity. RXR agonists (rexinoids) can improve glucose and lipid metabolism but earlier compounds often caused hypertriglyceridemia, hepatomegaly and suppression of the thyroid hormone axis. CNX-013-B2 is a heterodimer-selective rexinoid designed to activate RXR partners involved in metabolic control without triggering adverse effects. The literature on PubMed contains a single primary research article describing CNX-013-B2's pharmacology and several reviews or unrelated studies that cite this paper. The key studies and citations are summarised below.

Primary research study

CNX-013-B2 modulates nuclear receptors and improves metabolic parameters in rodents (2014)

Reference: Sadasivuni et al., *Diabetology & Metabolic Syndrome* (2014).

- **Aim and rationale:** The authors noted that many rexinoids increased triglycerides or caused hepatomegaly, so they designed CNX-013-B2, a potent and selective RXR agonist, to target partners that control insulin resistance [1]. Their goal was to evaluate whether the compound could treat multiple risk factors of metabolic syndrome without the side effects seen with earlier rexinoids [2].

- **Experimental design:** CNX-013-B2 was selected through a screening system to identify compounds that activate a chosen subset of RXR heterodimers [3]. Male C57BL/6J mice on a high-fat diet (DIO mice; n = 10) and ob/ob mice (n = 8) were treated orally with CNX-013-B2 (10 mg/kg twice daily) or vehicle for 10 weeks and 4 weeks, respectively [4]. Researchers measured plasma glucose, triglycerides, cholesterol, glycerol, free fatty acids, body weight, food intake, oral glucose tolerance, non-shivering thermogenesis and organ weights [4].

- **Mechanistic findings:** CNX-013-B2 selectively activated peroxisome proliferator-activated receptors (PPARs) α, β/δ and γ and modulated the activity of liver X receptor (LXR), thyroid hormone receptor (THR) and farnesoid X receptor (FXR) [5]. It therefore acted as a pan-PPAR activator while also influencing other nuclear receptors involved in metabolic regulation.

- **Metabolic outcomes:** In ob/ob mice, CNX-013-B2 lowered fed glucose by ~25 % ($p < 0.001$) and reduced serum total cholesterol by 14 % ($p < 0.05$) and LDL-cholesterol by 18 % ($p < 0.01$) [6]. In diet-induced obese mice, the compound reduced fasting glucose by 12 % ($p < 0.01$), fed triglycerides

by 20 %, and total cholesterol by 20 % [7]. These reductions were accompanied by improved insulin sensitivity, enhanced cold-induced thermogenesis and a 7 % reduction in body weight [8].

- **Safety observations:** Unlike earlier rexinoids, CNX-013-B2 did not cause hypertriglyceridemia, hepatomegaly or weight gain. The authors concluded that the compound is an orally bio-available rexinoid that could be used to manage multiple risk factors of metabolic syndrome without the side effects reported for other rexinoids [9].

- **Gene expression:** The paper's figures (not reproduced here) showed that CNX-013-B2 increased expression of genes involved in lipid metabolism and thermogenesis, such as ApoAII and ACOX1 in the liver and UCP-3 in muscle [10].

Reviews and other articles citing CNX-013-B2

Although no additional experimental studies on CNX-013-B2 were found in PubMed, several reviews and unrelated studies cite the 2014 paper to illustrate RXR-mediated metabolic effects.

Exercise mimetics and aging (systematic review, 2025)

A systematic review of exercise mimetics in aging summarised CNX-013-B2's properties as an example of a compound that mimics exercise-induced metabolic improvements. The authors noted that CNX-013-B2 binds and activates RXRs and selectively activates PPAR-α, β/δ and γ [11]. In obese mice, administration of the compound improved insulin sensitivity and glucose tolerance, reduced glycemic and lipid levels and significantly lowered body weight [11]. The review also highlighted that CNX-013-B2 modulates gene expression in multiple tissues: in liver it increases ApoAII, ACOX1, MDR3, SREBP1c and SCD1; in adipose tissue it up-regulates PPARγ, SREBP1c and SCD1; and in muscle it raises PDK4, DiO2 and UCP3 [12]. Because it exerts coordinated effects across several organs, the authors suggested that CNX-013-B2 could be useful as an exercise mimetic [13].

Review on endocrine-mediated metabolic disruption (2019) and obesity overview (2022)

A Frontiers in Endocrinology review on endocrine-mediated mechanisms of metabolic disruption listed CNX-013-B2 among compounds that act through RXR and PPAR pathways. In the reference section it cited the 2014 study and summarised its title, noting that CNX-013-B2 modulates several nuclear receptors and controls multiple metabolic risk factors without causing hypertriglyceridemia or hepatomegaly [14]. A comprehensive review on obesity and metabolic mechanisms similarly included the citation, emphasising that CNX-013-B2 acts as a pan-tissue rexinoid that improves metabolic outcomes in animal models [15]. Neither review presented new experimental data on CNX-013-B2; they referenced the 2014 paper as background when discussing RXR agonists and PPAR activators.

UAB126 study on obesity (2020)

A 2020 study described a different small molecule, UAB126, which reversed diet-induced obesity and associated metabolic disorders in mice. The paper cited the CNX-013-B2 study in its reference list, acknowledging prior work on rexinoids [16], but it did not test CNX-013-B2 itself. The focus was on UAB126's

effects on adiposity and glucose metabolism; CNX-013-B2 served solely as an example of earlier RXR/PPAR agonist research.

Exercise mimetic table and other reviews

The exercise mimetics review included a table of compounds that modulate sirtuin, AMPK, PGC-1 and PPAR pathways. In this table CNX-013-B2 was listed as acting on skeletal muscle, adipose tissue and liver, improving insulin sensitivity and glucose tolerance, lowering body weight and altering gene expression through PPAR activation [17]. Other review articles (e.g., on peroxisome proliferator-activated receptor agonists, endocrine disruptors and metabolic syndrome) also referenced CNX-013-B2 in their citations but did not provide additional experimental data. Conference abstracts (e.g., a 2014 Diabetes Research and Clinical Practice abstract titled *OP6 CNX-013-B2, a selective rexinoid provides robust control of hyperglycemia*) and late-breaking abstracts from the American Diabetes Association have not been archived on PubMed; available summaries mirror the findings reported in the 2014 paper.

Conclusion

The PubMed literature on CNX-013-B2 consists of a single experimental study and several secondary references. The 2014 rodent study demonstrated that CNX-013-B2 is a heterodimer-selective rexinoid that activates PPAR isoforms and other nuclear receptors, lowering glucose and lipid levels, improving insulin sensitivity and reducing body weight without the side effects associated with earlier rexinoids [18]. Subsequent reviews and unrelated research papers have cited this study to illustrate the potential of RXR-PPAR agonists for metabolic disorders [19] [14], but no additional experimental investigations of CNX-013-B2 were found. Further research would be necessary to verify its efficacy and safety in different models and to explore its mechanisms in greater detail.

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[1] [2] [3] [4] [5] [6] [7] [8] [9] [18] CNX-013-B2, a unique pan tissue acting rexinoid, modulates several nuclear receptors and controls multiple risk factors of the metabolic syndrome without risk of hypertriglyceridemia, hepatomegaly and body weight gain in animal models - PubMed
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[16] A Small Molecule, UAB126, Reverses Diet-Induced Obesity and its Associated Metabolic Disorders - PMC
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