REV-ERBα MITIGATES HEART FAILURE BY EXERTING TRANSCRIPTIONAL REPRESSION: A LITERATURE REVIEW

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Abstract

Heart failure (HF) is a major cause of mortality, affecting millions of people in the United States. Current treatments focus on minimizing stress and improving hemodynamics, but there is still a need for an effective strategy that can selectively inhibit the abnormal gene program associated with HF. Rev-erb, a member of the nuclear receptor superfamily, has been identified as a potential therapeutic target for HF due to its role in regulating circadian rhythm, glucose and lipid metabolism, and inflammation. Synthetic Rev-erb agonists have shown promise in preclinical studies, improving metabolic and inflammatory pathways while also enhancing mitochondrial function. Long-term therapy with these agonists has also been shown to reduce atherosclerotic plaque. While more research is needed to fully understand Rev-erb's functions in HF development, it represents a potentially exciting new avenue for treatment. This literature review explores the potential use of Rev-erb agonists as a therapeutic target for HF patients.

Keywords**:** Rev-erb, Heart Failure, Treatment, Novel Drug

Introduction

More than 5 million people in the United States suffer from heart failure (HF), and this number is increasing (1). Despite advancements in medical therapy, HF is associated with a 50% mortality rate within five years of diagnosis (2). The latest state-of-the-art treatment aims to minimize neurohormonal stress and improve hemodynamics. By reducing neurohormonal stress, which involves abnormal activation of hormones like adrenaline, treatment aims to alleviate strain on the heart and prevent further damage (3).

Improving hemodynamics, the forces involved in blood circulation, helps enhance the heart's pumping efficiency, ensuring better oxygen and nutrient delivery to tissues. These approaches collectively aim to enhance overall cardiac performance and mitigate the progression of heart failure, promoting better patient outcomes (3). Heart remodelling is strongly linked to a specific exchange of gene expression programs, which are mediated by major transcription factors (TFs) (4). Unfortunately, an effective HF treatment strategy is not yet available because it is unclear how to selectively inhibit the abnormal gene program coordinated by numerous TFs in a global manner, and treatments that directly target transcriptional regulation of the abnormal gene program are also lacking (1, 3).

Rev-erb, a member of the nuclear receptor superfamily, comprises two subgroups, Rev-erb (NR1D1) and (NR1D2), which control circadian rhythm, glucose and lipid metabolism, and inflammatory response. Recently, synthetic Rev-erb agonists, namely SR9009 and SR9011, were developed and shown to improve hyperglycaemia, dyslipidaemia, and skeletal muscle oxidative capacity by regulating mitochondrial number and oxidative activity. Furthermore, long-term SR9009 therapy was found to reduce atherosclerotic plaque by decreasing the ratio of proinflammatory M1 macrophages to anti-inflammatory M2 macrophages in low-density lipoprotein (LDL) receptor-deficient mice given a Western diet. As a result, Rev-erb is considered a promising therapeutic target for HF. However, little is known about Rev-erb's pathophysiological functions in the development of HF (5, 6).

This literature review aims to explore the potential use of Rev-erb agonists as a therapeutic target for HF patients.

Results and Discussions

What is Rev-erb agonist

Rev-erb is a nuclear receptor that belongs to the superfamily of ligand-activated TFs. It is a member of the orphan nuclear receptor subfamily, which means that its

endogenous ligand is currently unknown. Rev-erb is a key regulator of the circadian clock and is involved in regulating numerous physiological processes, including metabolism, inflammation, and cell proliferation (5, 6).

Initially, Rev-erb was used to treat sleep disorders and metabolic syndrome (7). However, over time there have been several recent studies showing the potential for using Reverb in reducing local inflammation, HF, and cancer (6, 7). Currently, two isoforms of Rev-erb have been found, namely Rev-erb α (NR1D1) and Rev-erb β (NR1D2). Rev-erb α was discovered in 1989 from the genomic origin of the avian erythroblastosis virus, while Rev-erb β was discovered in 1994 (7).

Rev-erb α and Rev-erb β are encoded by separate genes. Both isoforms share a similar structure and have a high degree of sequence homology, but they have slightly different functions and tissue distributions (7, 8). Rev-erb α is primarily expressed in the liver, adipose tissue, and skeletal muscle, and it plays a role in regulating glucose and lipid metabolism, as well as the circadian rhythm. Rev-erb β, on the other hand, is more widely expressed in various tissues, including the brain, heart, and immune cells, and it has been implicated in regulating inflammation and immune responses (8, 9).

Table 1: Current Rev-erb agonists research on the disease using experimental studies.

Authors	Current Rev-erb Agonists	Disease Model of study	Mechanisms
Pourcet et al. (2018) (10).	MCC950	Liver failure	NLRP3 inflammasome, Transcription of Nlrp3 and IL-1β.
Tao et al. (2019) (11).	GSK4112 (also known as SR6472)	Gastric carcinoma	Reduces glycolysis in human gastric carcinoma cells by inhibiting expressions of the genes encoding rate-limiting enzymes.
1. Sitaula et al. (2015) (12). 2. Reitz et al. (2015) (13). 3. Stujanna et al. (2017) (14).	SR9009	Heart failure, atherosclerotic plaque	Inhibits the expressions of natriuretic peptide, inflammatory cytokines, and MMP-9. Reduces infiltration of neutrophils and M1 macrophages into the infarcted myocardium.
Wolf et al. (2020) (15).	SR9011	Immune function of microglia	Inhibits mitochondrial respiration and metabolic gene expression, decreases phagocytosis in microglia.

Mechanism of actions

The precise mechanisms by which Rev-erb agonists improve heart function in HF patients are not yet fully understood. However, it is believed that Rev-erb agonists exert their effects through various metabolic and inflammatory pathways. In preclinical studies, Rev-erb agonists have been found to enhance glucose and lipid metabolism in skeletal muscle cells, which may help to alleviate some of the metabolic disturbances seen in HF patients. It enhances glucose utilization, counters insulin resistance, stimulates fatty acid oxidation, and contributes to mitochondrial regulation. These actions collectively improve energy metabolism, offering potential therapeutic benefits for individuals with heart failure, though clinical validation is required (16, 17). These compounds have also been shown to reduce inflammation by suppressing the expression of proinflammatory genes in macrophages such as Nlrp3, IL-6, IL-1β, IL-18, Tnfα, Ccl2, TLR4, Mmp9, and Cx3cr1 (7, 16).

Furthermore, Rev-erb agonists have been found to improve mitochondrial function in skeletal muscles. Rev-erb agonists may promote the generation of new mitochondria, a process known as mitochondrial biogenesis. This could lead to an overall increase in mitochondrial content within skeletal muscle cells, thereby improving their energy production capacity (17, 18). Rev-erb is also involved in the regulation of circadian rhythms, including those related to metabolism. Mitochondrial function is intricately linked to circadian rhythms, and Rev-erb agonists could modulate these rhythms to optimize mitochondrial activities (17). Mitochondrial dysfunction has been linked to the development of HF. By enhancing mitochondrial function, Rev-erb agonists may help to preserve cardiac function and prevent further deterioration in HF patients (17).

Additionally, Rev-erb agonists may have potential as a treatment for atherosclerosis, which is a common comorbidity in HF patients (19). This effect is achieved by reducing the ratio of proinflammatory M1 macrophages to anti-inflammatory M2 macrophages within the plaque. By decreasing the ratio of M1 to M2 macrophages, there is a shift towards an anti-inflammatory environment. This reduction in inflammation is crucial for limiting the damage caused by inflammatory mediators and cytokines in the arterial wall. The shift from M1 to M2 macrophages indicates a change in the functional phenotype of the macrophage population (17, 18). M2 macrophages are associated with tissue repair, resolution of inflammation, and maintenance of tissue homeostasis. This shift may contribute to a more favourable microenvironment within the plaque (17). Overall, Rev-erb agonists have the potential to improve heart function in HF patients through various metabolic and inflammatory pathways. However, more research is needed to fully understand the mechanisms by which these compounds exert their effects (18).

Rev-erb as a potential treatment for HF patients

Rev-erb agonists have shown potential as a treatment for HF due to their ability to improve various metabolic and inflammatory pathways. In preclinical studies, treatment with SR9009 and SR9011 were found to enhance glucose and lipid metabolism in skeletal muscle cells This potential enhancement suggests a possible alleviation of metabolic disruptions observed in patients with HF. Additionally, these compounds exhibited anti-inflammatory effects by inhibiting proinflammatory gene expression and encouraging the expression of anti-inflammatory genes in macrophages (7, 16).

In addition to their effects on metabolism and inflammation, Rev-erb agonists have been found to enhance mitochondrial function in skeletal muscles. This is important because impaired mitochondrial function has been linked to the development of HF. Rev-erb agonists have been shown to promote mitochondrial biogenesis, which is the process of generating new mitochondria within cells. This is important because an increased number of healthy mitochondria can enhance the overall capacity of cells, including skeletal muscles, to produce energy. In turn, this can positively impact the energy balance of the entire body, including the heart (8, 20). By improving mitochondrial function, Rev-erb agonists may help to preserve cardiac function and prevent further deterioration in HF patients (17, 20).

Long-term treatment with SR9009 has also been shown to reduce atherosclerotic plaque in LDL receptor-deficient mice fed a Western diet. This was achieved through a decrease in the ratio of proinflammatory M1 macrophages to anti-inflammatory M2 macrophages in the plaque. This suggests that Rev-erb agonists may have potential as a treatment for atherosclerosis, which is a common co-morbidity in HF patients (13).

Despite these promising findings, more research is needed to fully understand the mechanisms by which Rev-erb agonists improve heart function in HF. Clinical trials are needed to determine the optimal dose and duration of treatment and assess the safety and efficacy of Rev-verb agonists in humans. Nonetheless, Rev-erb agonists represent a potentially exciting new avenue for the treatment of HF (21).

Advantages and disadvantages

Rev-erb agonists, such as SR9009 and SR9011, have been found to have potential benefits for various conditions, including HF. However, like any medication, there are advantages and disadvantages to their use. Rev-erb agonists have been shown to improve glucose and lipid metabolism, making them potentially useful in treating conditions like type 2 diabetes and dyslipidaemia (14). By regulating mitochondrial number and oxidative activity, Rev-erb agonists can help improve skeletal muscle oxidative capacity, which may have benefits for conditions such as muscle wasting and sarcopenia (8). Long-term use of Rev-erb agonists has been shown to reduce atherosclerotic plaque by decreasing the ratio of proinflammatory M1 macrophages to anti-inflammatory M2 macrophages (14, 23).

While Rev-erb agonists show potential benefits for various conditions, little is known about Rev-erb's full functions, particularly in the context of HF. Rev-erb agonists have shown positive effects in preclinical studies, potential side effects, such as liver toxicity, have been reported in animal studies (24). While preclinical studies have shown promising results, there is limited clinical evidence to support the effectiveness of Rev-erb agonists in humans, and more research is needed to establish their safety and efficacy (24).

Table 2: Biochemical Features of Changes in Heart Failure in study.

References	Rev-Erb Agonist	Biochemical Features Changes
Sitaula et al. (2015) (12).	SR9009	Impairs the appearance of pro-inflammatory M1 phenotype (M1 macrophages such as iNos, Tnfa, CD80, CD86, inflammatory cytokines IL-6, IL-1b, and chemokines Mif, Mip1a, Mip1b, Mcp-1 were significantly reduced). Enhance anti-inflammatory M2 phenotype (Ym1, Ym2, and Mr).
Reitz et al. (2015) (13).	SR9009	Downregulation of cardiac NLRP3, IL-1β, and IL-18. These are critical constituents of the NLRP3 inflammasome.
Stujanna et al. (2017) (14).	SR9009	Decreased IL-6 and MCP-1 production, MMP-9 expression, NF-κB and MAPKs activations, and neutrophil/M1 macrophage infiltrations in infarct and border myocardium during the acute phase of MI. Suppression of NF-κB, ERK, or p38 signalling pathway, leading to inhibition of the vicious circle of proinflammatory amplification, the development of adverse LV remodelling, and cardiac rupture.
Solt et al. (2012) (22).	SR9011	Suppressed the circadian rhythm of Nampt gene expression in the liver. Alter post-translational acetylation of proteins. 5% increase in oxygen consumption (VO2) is increased. VO2 increasing was not due to increased activity since mice displayed a 15% decrease in movement.

Future studies

Further research is necessary to comprehend the specific mechanisms by which Rev-erb agonists improve heart function in HF. This includes understanding how they affect gene expression, mitochondrial function, and inflammation. To evaluate the safety and effectiveness of Rev-erb agonists in treating HF, additional clinical trials should be conducted.

These trials should assess both short-term and long-term effects of treatment, as well as potential side effects. It is also important to determine the optimal dose and duration of treatment for Rev-erb agonists in HF patients and whether combining them with other HF treatments would be beneficial. To compare the efficacy and safety of Rev-erb agonists with other HF treatments, Rev-erb agonists should be studied alongside established treatments.

Table 3: Rev-erb agonist in heart failure treatment.

Authors	Drug	Dose	Study Population	Treatment Duration	Mechanism of action	Outcome
Sitaula et al. (2015) (12).	SR9009 was formulated in 15% cremophor.	100 mg/kg/ day intra-peritoneal	20 homozygous LDL receptor deficient ($ldlr^{-/-}$) male mice at the age of 7 weeks	7 weeks	Reduced the polarization of BMDMs to proinflammatory M1 macrophage while increasing the polarization of BMDMs to anti-inflammatory M2 macrophages.	Significantly lowered atherosclerotic plaque by 23% compared to the control mice.
Reitz et al. (2015) (13).	SR9009 was formulated in 15% cremophor.	100 mg/kg/ day intra-peritoneal	C57BL6 mice (Charles River) at the age of 8 weeks	5 days	Reduce the cardiac NLRP3 inflammasome, decreasing immunocyte recruitment, allowing the vulnerable infarct to heal and promotes efficient repair.	Long-term cardiac repair post-myocardial ischemia reperfusion in mice.
Stujanna et al. (2017) (14).	SR9009 dissolved in 1% dimethyl sulfoxide (DMSO) in normal saline.	100 mg/kg/ day intra-Peritoneal	165 male wild-type C57BL6 mice at the age of 12-14 weeks	From 1 day before surgery to 7 days after surgery	Inhibits the expressions of natriuretic peptide, inflammatory cytokines, and MMP-9. Reduces infiltration of neutrophils and M1 macrophages into the infarcted myocardium.	Improved LV function and survival after MI.
Solt et al. (2012) (22).	SR9011	100 mg/ kg/ intra-peritoneal b.i.d	C57BL6 mice at the age of 9-10 weeks	12 days	Suppressed the circadian rhythm of Nampt gene expression in the liver. Alter post-translational acetylation of proteins. Oxygen consumption (VO2) is increased.	Decreased lipogenesis and cholesterol / bile acid synthesis in the liver, increased lipid and glucose oxidation in the skeletal muscle, and decreased triglyceride synthesis and storage in the white adipose tissue

Biomarkers can be used to identify patients who would benefit from Rev-erb agonist treatment and monitor their response to therapy. Elevated levels of Brain Natriuretic Peptide (BNP) and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) indicate heart stress in HF. Troponin (cTnT, cTnI) signals myocardial damage, while C-reactive protein (CRP) suggests inflammation. Growth Differentiation Factor-15 (GDF-15) and Soluble ST2 (sST2) elevations link to adverse outcomes, cardiac stress, and fibrosis in HF. Galectin-3 indicates cardiac fibrosis. Uric acid elevation may link to oxidative stress (25). Renal function markers (serum creatinine, BUN) monitor HF's impact on kidneys. Low albumin indicates malnutrition and poor HF prognosis. Elevated myoglobin, Neutrophil-to-Lymphocyte Ratio (NLR), and Red Cell Distribution Width (RDW) associate with myocardial injury, inflammation, and increased HF mortality, respectively (26). Future research should focus on evaluating potential biomarkers of Rev-erb agonist response in HF patients.

Conclusion

In conclusion, HF remains a significant public health problem, and current therapies have limited success in improving patient outcomes. The development of novel therapeutic approaches that can improve the abnormal gene program coordinated by numerous TFs in a global manner is urgently needed. Rev-erb agonists, such as SR9009 and SR9011, have shown promise in preclinical studies and offer a potential new avenue for HF treatment. However, more research is required to determine the precise mechanisms by which these agonists improve heart function and their long-term safety and effectiveness in humans.

Clinical trials assessing the optimal dose, duration, and combination of Rev-erb agonists with other HF treatments are needed to determine their therapeutic potential. Furthermore, biomarker development could identify patients who would benefit most from Rev-erb agonist therapy and enable the monitoring of treatment response. The use of Rev-erb agonists as a therapeutic target for HF patients offers exciting possibilities and deserves further investigation.

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Not applicable.

Competing interest

The authors declare that there is no conflict of interest.

Ethical Clearance

This research was a literature review study and did not involve human subjects; therefore, no ethical clearance was required.

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